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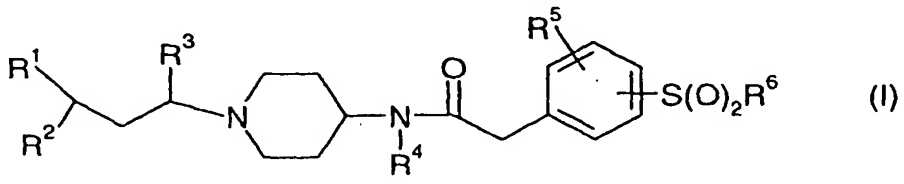
(54) Title: PIPERIDINE DERIVATIVES AND THEIR USE AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY (ESPECIALLY CCR5)



(I)

(57) Abstract: Compounds of formula (I): compositions comprising them, processes for preparing them and their use in medical therapy (for example modulating CCR5 receptor activity in a warm blooded animal).

PIPERIDINE DERIVATIVES AND THEIR USE AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY (ESPECIALLY CCR5)

The present invention relates to heterocyclic derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in PCT/SE01/01053, EP-A1-1013276, WO00/08013, WO99/38514 and WO99/04794.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important rôle in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are á growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

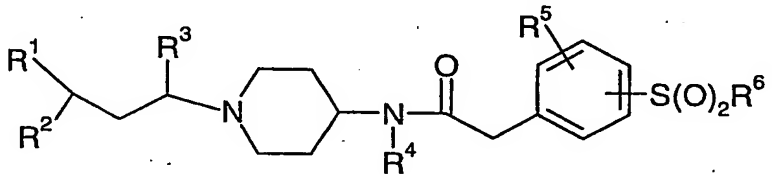
The CCR5 receptor is expressed on T-lymphocytes, monocytes, macrophages, dendritic cells, microglia and other cell types. These detect and respond to several

chemokines, principally "regulated on activation normal T-cell expressed and secreted" (RANTES), macrophage inflammatory proteins (MIP) MIP-1α and MIP-1β and monocyte chemoattractant protein-2 (MCP-2).

This results in the recruitment of cells of the immune system to sites of disease. In many diseases it is the cells expressing CCR5 which contribute, directly or indirectly, to tissue damage. Consequently, inhibiting the recruitment of these cells is beneficial in a wide range of diseases.

CCR5 is also a co-receptor for HIV-1 and other viruses, allowing these viruses to enter cells. Blocking the receptor with a CCR5 antagonist or inducing receptor internalisation with a CCR5 agonist protects cells from viral infection.

The present invention provides a compound of formula (I):



(I)

wherein:

R^1 is phenyl {para-substituted by: halo, hydroxy, nitro, $S(O)_k(C_{1-6}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-6}$ alkyl), $S(O)_2N(C_{1-6}$ alkyl)$_2$, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, $C(O)NH_2$, $C(O)NH(C_{1-6}$ alkyl), $C(O)N(C_{1-6}$ alkyl)$_2$, C(O)[N-linked heterocyclyl], CO_2H, $CO_2(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), $C(O)(C_{1-6}$ alkyl), CF_3, OCF_3, phenyl, heteroaryl, (C_{1-4} alkyl)phenyl, (C_{1-4} alkyl)heteroaryl, NHC(O)phenyl, NHC(O)heteroaryl, NHC(O)(C_{1-4} alkyl)phenyl, NHC(O)(C_{1-4} alkyl)heteroaryl, $NHS(O)_2$phenyl, $NHS(O)_2$heteroaryl, $NHS(O)_2(C_{1-4}$ alkyl)phenyl, $NHS(O)_2(C_{1-4}$ alkyl)heteroaryl, $NHC(O)NH(C_{1-6}$ alkyl), $NHC(O)NH(C_{3-7}$ cycloalkyl), NHC(O)NHphenyl, NHC(O)NHheteroaryl, NHC(O)NH(C_{1-4} alkyl)phenyl or NHC(O)NH(C_{1-4} alkyl)heteroaryl; wherein the foregoing phenyl and heteroaryl groups are optionally substituted by halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3};

R^2 is phenyl or heteroaryl, either of which is optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3;

R^3 is hydrogen or C_{1-4} alkyl;

R^4 is ethyl, allyl or cyclopropyl;

R^5 is hydrogen, halo, hydroxy, nitro, $S(O)_m(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3;

R^6 is C_{1-4} alkyl;

k, m and n are, independently, 0, 1 or 2;

or a pharmaceutically acceptable salt thereof or a solvate thereof;

provided that:

- when R^3 and R^5 are both hydrogen, R^4 is ethyl, R^6 is para-$(S(O)_2CH_3)$ and R^2 is unsubstituted phenyl then R^1 is not para-methoxy-phenyl, para-methyl-phenyl, para-trifluoromethyl-phenyl or 3,4-dichlorophenyl;
- when R^3 and R^5 are both hydrogen, R^4 is ethyl, R^6 is para-$(S(O)_2CH_3)$ and R^2 is unsubstituted phenyl, pyrid-2-yl or pyrid-4-yl then R^1 is not para-chloro-phenyl; and,
- when R^3 and R^5 are both hydrogen, R^6 is para-$(S(O)_2CH_3)$ and R^2 is meta-chloro-phenyl, unsubstituted phenyl or thiophen-3-yl then R^1 is not para-fluoro-phenyl.

Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts (adducts) such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or, additionally, formate. Acid addition salt is, for example hydrochloride or formate.

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates.

Alkyl groups and moieties are straight or branched chain and are, for example, methyl (sometimes abbreviated to Me), ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl or tert-butyl.

Cycloalkyl is for example, cyclopropyl, cyclopentyl or cyclohexyl.

N-Linked heterocyclyl is a nitrogen-linked, non-aromatic 3, 4, 5 or 6 membered ring optionally comprising one further heteroatom (selected from the group comprising nitrogen, oxygen and sulphur). It is, for example, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or thiomorpholinyl.

Heteroaryl is an aromatic 5 or 6 membered ring, optionally fused to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur; or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Heteroaryl is, for example, furyl, thienyl (also known as thiophenyl), pyrrolyl, thiazolyl, isothiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, [1,2,4]-triazolyl, pyridinyl, pyrimidinyl, indolyl, benzo[b]furyl (also known as benzfuryl), benz[b]thienyl (also known as benzthienyl or benzthiophenyl), indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 1,2,3-benzothiadiazolyl, an imidazopyridinyl (such as imidazo[1,2a]pyridinyl), thieno[3,2-b]pyridin-6-yl, 1,2,3-benzoxadiazolyl (also known as benzo[1,2,3]thiadiazolyl), 2,1,3-benzothiadiazolyl, benzofurazan (also known as 2,1,3-benzoxadiazolyl), quinoxalinyl, a pyrazolopyridine (for example 1H-pyrazolo[3,4-b]pyridinyl), quinolinyl, isoquinolinyl, a naphthyridinyl (for example [1,6]naphthyridinyl or [1,8]naphthyridinyl), a benzothiazinyl or dibenzothiophenyl (also known as dibenzothienyl); or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Heteroaryl is especially pyridyl, pyrimidinyl, indolyl or benzimidazolyl.

(C_{1-4} Alkyl)phenyl is, for example, benzyl, 2-phenylethyl or 1-phenyleth-1-yl. (C_{1-4} Alkyl)heteroaryl is, for example, pyridylmethyl or pyrimidinylmethyl. NHC(O)Heteroaryl is, for example, NHC(O)pyridyl. NHC(O)(C_{1-4} Alkyl)phenyl is, for example, NHC(O)benzyl. NHC(O)(C_{1-4} Alkyl)heteroaryl is, for example, NHC(O)CH_2pyridyl. NHS(O)$_2$Heteroaryl is, for example, NHS(O)$_2$pyridyl. NHS(O)$_2$(C_{1-4} Alkyl)phenyl is, for example, NHS(O)$_2$benzyl. NHS(O)$_2$(C_{1-4} Alkyl)heteroaryl is, for example, NHS(O)$_2$$CH_2$pyridyl. NHC(O)NHheteroaryl is, for example, NHC(O)NHpyridyl. NHC(O)NH(C_{1-4} Alkyl)phenyl is, for example, NHC(O)NHbenzyl. NHC(O)NH(C_{1-4} Alkyl)heteroaryl is, for example, NHC(O)NHCH_2pyridyl.

In one aspect of the invention k, m and n are, independently, 0 or 2. In a further aspect of the invention k, m and n are all 2.

In another aspect of the invention R^1 is phenyl {para-substituted by: halo, S(O)$_k$(C_{1-6} alkyl), S(O)$_2$$NH_2$, S(O)$_2$NH($C_{1-6}$ alkyl), S(O)$_2$N(C_{1-6} alkyl)$_2$, cyano, NH_2, NH(C_{1-6} alkyl), N(C_{1-6} alkyl)$_2$, CO_2(C_{1-6} alkyl), NHC(O)(C_{1-6} alkyl), NHC(O)O(C_{1-6} alkyl), NHS(O)$_2$(C_{1-6} alkyl), NHC(O)phenyl, NHC(O)heteroaryl, NHC(O)(C_{1-4} alkyl)phenyl, NHC(O)(C_{1-4} alkyl)heteroaryl, NHS(O)$_2$phenyl, NHS(O)$_2$heteroaryl, NHS(O)$_2$(C_{1-4} alkyl)phenyl, NHS(O)$_2$(C_{1-4} alkyl)heteroaryl, NHC(O)NH(C_{1-6} alkyl), NHC(O)NH(C_{3-7} cycloalkyl), NHC(O)NHphenyl, NHC(O)NHheteroaryl, NHC(O)NH(C_{1-4} alkyl)phenyl or NHC(O)NH(C_{1-4} alkyl)heteroaryl; wherein the foregoing phenyl and heteroaryl groups are optionally

substituted by halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3, [especially optionally substituted by halo]}. The variable k is 2.

In a further aspect of the invention R^1 is phenyl {para-substituted by: halo, cyano, $CO_2(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), NHC(O)phenyl, NHC(O)heteroaryl, $NHC(O)(C_{1-4}$ alkyl)phenyl, $NHC(O)(C_{1-4}$ alkyl)heteroaryl, $NHS(O)_2$phenyl, $NHS(O)_2$heteroaryl, $NHS(O)_2(C_{1-4}$ alkyl)phenyl or $NHS(O)_2(C_{1-4}$ alkyl)heteroaryl; wherein the foregoing phenyl and heteroaryl groups are optionally substituted by halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3, [especially optionally substituted by halo]}. The variable k is 2.

In a still further aspect of the invention R^1 is phenyl {para-substituted by: halo, cyano, $CO_2(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), $NHC(O)(C_{1-4}$ alkyl)phenyl, $NHC(O)(C_{1-4}$ alkyl)heteroaryl, $NHS(O)_2(C_{1-4}$ alkyl)phenyl or $NHS(O)_2(C_{1-4}$ alkyl)heteroaryl; wherein the foregoing phenyl and heteroaryl groups are optionally substituted by halo}.

In another aspect R^1 is phenyl para-substituted by $S(O)_k(C_{1-4}$ alkyl), wherein k is 0, 1 or 2, (for example SCH_3, $S(O)CH_3$ or $S(O)_2CH_3$), $NHS(O)_2(C_{1-4}$ alkyl) (for example $NHS(O)_2CH_3$) or $NHC(O)(C_{1-4}$ alkyl) (for example $NHC(O)CH_3$). In yet another aspect R^1 is phenyl para-substituted by $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$), $NHS(O)_2(C_{1-4}$ alkyl) (for example $NHS(O)_2CH_3$) or $NHC(O)(C_{1-4}$ alkyl) (for example $NHC(O)CH_3$). In a still further aspect R^1 is phenyl para-substituted by $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$).

In a further aspect of the invention R^2 is phenyl or heteroaryl, either of which is optionally substituted in the ortho or meta position (that is ortho or meta to the point of attachment of the R^2 ring to the the rest of the structure of formula (I)) by halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3.

In another aspect of the invention R^2 is phenyl or heteroaryl, either of which is optionally substituted in the ortho or meta position (that is ortho or meta relative to the position of attachment of that ring to the structure of formula (I)) by halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3; wherein n is 0, 1 or 2, for example 0 or 2.

In yet another aspect R^2 is optionally substituted phenyl (especially optionally substituted by halo (such as chloro or fluoro), cyano, methyl, ethyl, methoxy, ethoxy or CF_3). In one aspect said substitution is on the ortho or meta position of the phenyl ring.

In a further aspect R^2 is optionally substituted phenyl (especially optionally substituted by halo or CF_3). For example R^2 is 3-fluorophenyl, 3-chlorophenyl, 4-fluorophenyl or 4-CF_3-phenyl.

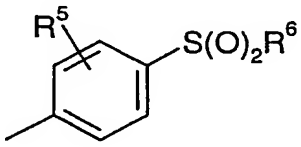
In a still further aspect R^2 is phenyl, mono-fluorophenyl (for example 3-fluorophenyl or 4-fluorophenyl), difluorophenyl (for example 3,4-difluorophenyl or 3,5-dofluorophenyl), mono-chlorophenyl (for example 3-chlorophenyl) or mono-(C_{1-4} alkoxy)phenyl (for example 4-methoxyphenyl). In a still further aspect R^2 is phenyl or mono-fluorophenyl (for example 3-fluorophenyl or 4-fluorophenyl).

In another aspect of the invention R^3 is hydrogen or methyl. When R^3 is C_{1-4} alkyl (such as methyl) the carbon to which R^3 is attached has, for example, the R absolute configuration. In yet another aspect of the invention R^3 is hydrogen. In a further aspect of the invention R^3 is methyl.

In a still further aspect of the invention R^4 is ethyl.

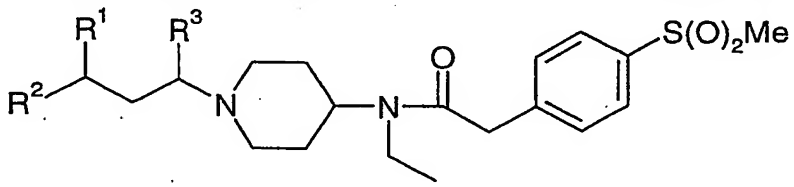
In another aspect of the invention R^5 is hydrogen, halo, hydroxy, nitro, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 or OCF_3. In a further aspect R^5 is hydrogen.

In a still further aspect of the invention R^6 is methyl or ethyl (such as methyl). A compound of the invention wherein R^6 is methyl. A compound of the invention wherein the $S(O)_2R^6$ group of formula (I) is para disposed to the remainer of the structure of formula (I), that is, it is as shown here:



In another aspect of the invention R^6 is C_{1-4} alkyl and wherein the $S(O)_2R^6$ group of formula (I) is para disposed to the remainder of the structure of formula (I).

In a still further aspect the present invention provides a compound of formula (Ia):



(Ia)

wherein R^1, R^2 and R^3 are as defined above; provided that:

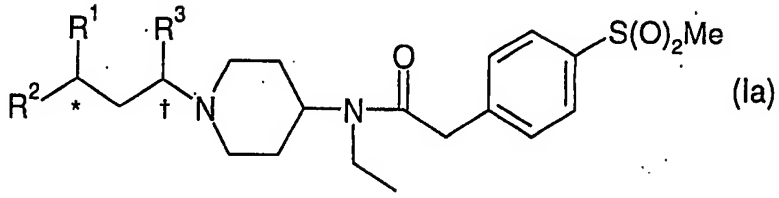
- when R^3 is hydrogen and R^2 is unsubstituted phenyl then R^1 is not para-methoxy-phenyl, para-methyl-phenyl or para-trifluoromethyl-phenyl;
- when R^3 is hydrogen and R^2 is unsubstituted phenyl, pyrid-2-yl or pyrid-4-yl then R^1 is not para-chloro-phenyl;
- when R^3 is hydrogen and R^2 is unsubstituted phenyl then R^1 is not 3,4-dichlorophenyl; and,
- when R^3 is hydrogen and R^2 is meta-chloro-phenyl, unsubstituted phenyl or thiophen-3-yl then R^1 is not para-fluoro-phenyl.

The present invention further provides a compound of formula (I) or (Ia) wherein R^1 is phenyl para-substituted by $S(O)_2(C_{1-4}$ alkyl) (such as $S(O)_2CH_3$); R^2 is phenyl or mono-fluorophenyl (such as 3-fluorophenyl); and R^3 is hydrogen or C_{1-4} alkyl (such as methyl) (R^3 is, for example, hydrogen); said compound being in free base form or in the form of a hydrochloride adduct.

The following compounds illustrate the invention.

TABLE I

Table I comprises compounds of formula (Ia).



(Ia)

Compound No.	R^1	R^2	R^3	Adduct	* Chirality	† Chirality	LCMS (MH+)
1	4-Chlorophenyl	Pyrid-3-yl	H				554
2	4-Chlorophenyl	Phenyl	H		(–) isomer #		553
3	4-Cyanophenyl	Phenyl	H				544
4	4-Methoxycarbonylphenyl	Phenyl	H				577
5	4-(Morpholin-4-ylcarbonyl)phenyl	Phenyl	H				632
6	4-Carboxamidophenyl	Phenyl	H				562
7	4-iso-propoxycarbonylphenyl	Phenyl	H				605
8	4-Fluorophenyl	Phenyl	H				
9	4-Aminophenyl	Phenyl	H				534
10	4-tert-butyloxycarbonylaminophenyl	Phenyl	H				634
11	4-(Pyridin-2-ylacetylamino)phenyl	Phenyl	H				653
12	4-(Pyridin-3-ylacetylamino)phenyl	Phenyl	H				653
13	4-(Pyridin-4-ylacetylamino)phenyl	Phenyl	H				653

14	4-Phenylacetylaminophenyl	Phenyl	H				652
15	4-Butyrylaminophenyl	Phenyl	H				604
16	4-Acetylaminophenyl	Phenyl	H				576
17	4-Cyclohexylureidophenyl	Phenyl	H				659
18	4-Phenylureidophenyl	Phenyl	H				653
19	4-Benzoylaminophenyl	Phenyl	H				638
20	4-(4-Chlorobenzoylamino)phenyl	Phenyl	H				672
21	4-(2,2-Dimethylpropionylamino)phenyl	Phenyl	H				618
22	4-Phenylmethanesulfonylamino-phenyl	Phenyl	H				688
23	4-Ethanesulfonylaminophenyl	Phenyl	H				626
24	4-Methanesulfonylaminophenyl	Phenyl	H				612
25	4-Phenylphenyl	Phenyl	H				595
26	4-Chlorophenyl	3-Fluorophenyl	H				571
27	4-Chlorophenyl	3-Fluorophenyl	Methyl			*R* isomer	585
28	4-Benzenesulfonylaminophenyl	Phenyl	H				675
29	4-iso-propylsulfonylaminophenyl	Phenyl	H				
30	4-Cyanophenyl	Phenyl	Methyl			*R* isomer	
31	4-Cyanophenyl	3-Fluorophenyl	Methyl			*R* isomer	

32	4-Methanesulfonylaminophenyl	Phenyl	Methyl			*R* isomer	
33	4-Methanesulfonylaminophenyl	3-Fluorophenyl	Methyl			*R* isomer	
34	4-Acetylaminophenyl	Phenyl	Methyl			*R* isomer	
35	4-Acetylaminophenyl	3-Fluorophenyl	Methyl			*R* isomer	
36	4-Chlorophenyl	Thien-2-yl	H				
37	4-Cyanophenyl	Thien-2-yl	H				
38	4-Chlorophenyl	Thiazol-4-yl	H				
39	4-Cyanophenyl	Thiazol-4-yl	H				
40	4-Methanesulfonylphenyl	Phenyl	H				597
41	4-Methanethiophenyl	Phenyl	H				565
42	4-iso-propylaminocarboxy-aminophenyl	Phenyl	H				619
43	4-tert-butoxycarbonylaminophenyl	3-Fluorophenyl	H				652
44	4-Aminophenyl	3-Fluorophenyl	H	hydrochloride			552
45	4-Acetylaminophenyl	3-Fluorophenyl	H				594
46	4-Methanesulfonylaminophenyl	3-Fluorophenyl	H				630
47	4-(4-Methanesulfonylbenzoylamino)-phenyl	3-Fluorophenyl	H	hydrochloride			734
48	4-(5-Methanesulfonylthien-2-yl-acetylamino)phenyl	3-Fluorophenyl	H	hydrochloride			740

49	4-Methanesulfonylaminophenyl	3-Fluorophenyl	H	hydrochloride	(+) isomer †		630
50	4-Methanesulfonylphenyl	Phenyl	H	hydrochloride	S isomer		597
51	4-Methanesulfonylphenyl	3-Fluorophenyl	H	hydrochloride	R isomer		615
52	4-Methanesulfonylphenyl	4-Fluorophenyl	H	hydrochloride	S isomer		615
53	4-Methanesulfonylphenyl	3-Chlorophenyl	H	hydrochloride	R isomer		631
54	4-Methanesulfonylphenyl	3,4-Difluorophenyl	H	hydrochloride	R isomer		633
55	4-Methanesulfonylphenyl	4-Methoxyphenyl	H	hydrochloride	S isomer		627
56	4-Methanesulfonylphenyl	3,5-Difluorophenyl	H	hydrochloride	R isomer		633
57	4-Methanesulfonylphenyl	Phenyl	Methyl		S isomer	R isomer	
58	4-Methanesulfonylphenyl	4-Fluorophenyl	Methyl		S isomer	R isomer	
59	4-Methanesulfonylphenyl	3,4-Difluorophenyl	Methyl		R isomer	R isomer	
60	4-Methanesulfonylphenyl	3,5-Difluorophenyl	Methyl		R isomer	R isomer	
61	4-Methanesulfonylphenyl	3-Fluorophenyl	Methyl		R isomer	R isomer	
62	4-Methanesulfonylphenyl	3-Trifluoromethylphenyl	Methyl		R isomer	R isomer	
63	4-Methanesulfonylphenyl	3-Trifluoromethylphenyl	H		R isomer		
64	4-Aminophenyl	3-Fluorophenyl	H				
65	4-(4-Methanesulfonylbenzoylamino)-phenyl	3-Fluorophenyl	H				
66	4-(5-Methanesulfonylthien-2-yl-acetylamino)phenyl	3-Fluorophenyl	H				

67	4-Methanesulfonylaminophenyl	3-Fluorophenyl	H		(+) isomer †		
68	4-Methanesulfonylphenyl	Phenyl	H		S isomer		
69	4-Methanesulfonylphenyl	3-Fluorophenyl	H		R isomer		
70	4-Methanesulfonylphenyl	4-Fluorophenyl	H		S isomer		
71	4-Methanesulfonylphenyl	3-Chlorophenyl	H		R isomer		
72	4-Methanesulfonylphenyl	3,4-Difluorophenyl	H		R isomer		
73	4-Methanesulfonylphenyl	4-Methoxyphenyl	H		S isomer		
74	4-Methanesulfonylphenyl	3,5-Difluorophenyl	H		R isomer		
75	4-Methanesulfinylpheny	Phenyl	H				

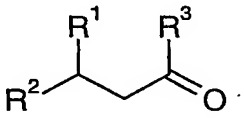
Compound separated from racemate using 10 micron Chiralcel OJ (250mm x 20mm). As eluent comprises formic acid compound from column is formic acid adduct which was treated with base to yield free base, Compound No.2. Estimated α D -7.29 ($CHCl_3$, 589nm, c=0.425)

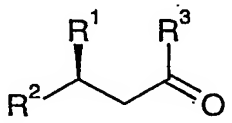
† Compound separated from racemate using 10 micron Chiralcel OJ (250mm x 20mm). As eluent comprises formic acid compound from column is formic acid adduct which was treated with base to yield free base, Compound 67. Compound No. 67 used to form Compound 49. Estimated α D +5.85 ($CHCl_3$, 589nm, c=2.00) for Compound No. 49.

In another aspect the present invention provides each individual compound recited in Table I. In yet another aspect the present invention provides Compound No. 2 of Table I, or a pharmaceutically acceptable salt thereof or a solvate thereof; Compound No. 50, 51, 67 or 68 of Table I, or a pharmaceutically acceptable salt thereof or a solvate thereof.

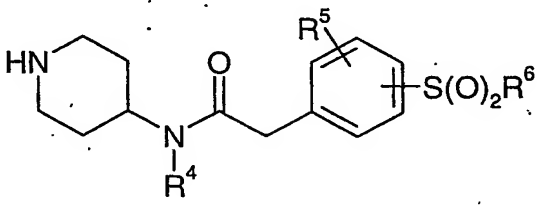
The compounds of the invention can be prepared as shown in the processes on pages marked Schemes 2 to 4 below, while Scheme 1 shows the preparation of an intermediate used in Schemes 2 and 3. (In Schemes 1 to 4 PG is a protecting Group; Ac is acetyl; Bn is benzyl, Bz is benzoyl; LDA is lithium diisopropylamide; and TMEDA is *N,N,N',N'*-tetramethylethyenediamine. Suitable coupling agents include PyBrOP or HATU.)

A compound of the invention can be prepared by reductive amination of a compound of formula (II) or (IIa):


(II)

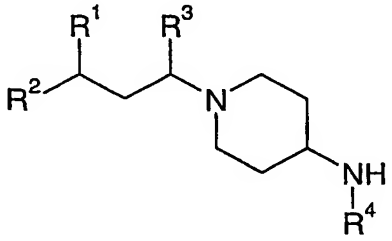

(IIa)

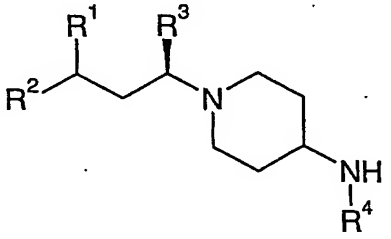
with a compound of formula (III):


(III)

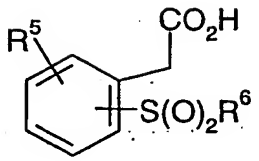
in the presence of $NaBH(OAc)_3$ (wherein Ac is $C(O)CH_3$) and acetic acid, in a suitable solvent (such as a C_{1-6} aliphatic alcohol, for example ethanol) at room temperature (for example 10-30°C)

Alternatively, a compound of the invention can be prepared by coupling a compound of formula (IV) or (IVa):


(IV)


(IVa)

with a compound of formula (V):



(V)

in the presence of a suitable coupling agent (for example PyBrOP or HATU) in the presence of a suitable base (such as a tertiary amine, for example diisopropylethylamine) in a suitable solvent (for example *N*-methylpyrrolidinone or a chlorinated solvent, such as dichloromethane) at room temperature (for example 10-30°C).

The starting materials for these preparative methods and Schemes are either commercially available or can be prepared by literature methods, adapting literature methods or by following or adapting Methods herein described.

In a further aspect the invention provides processes for preparing the compounds of the invention. Many of the intermediates in the processes are novel and these are provided as further features of the invention.

The compounds of the invention have activity as pharmaceuticals, in particular as modulators (such as agonists, partial agonists, inverse agonists or antagonists) of chemokine receptor (especially CCR5) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

The compounds of the present invention are also of value in inhibiting the entry of viruses (such as human immunodeficiency virus (HIV)) into target calls and, therefore, are of value in the prevention of infection by viruses (such as HIV), the treatment of infection by viruses (such as HIV) and the prevention and/or treatment of acquired immune deficiency syndrome (AIDS).

According to a further feature of the invention there is provided a compound of the invention, or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in a method of treatment of a warm blooded animal (such as man) by therapy (including prophylaxis).

According to a further feature of the present invention there is provided a method for modulating chemokine receptor activity (especially CCR5 receptor activity) in a warm blooded animal, such as man, in need of such treatment, which comprises administering to

said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof or a solvate thereof.

The present invention also provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof or a solvate thereof, as a medicament, especially a medicament for the treatment of transplant rejection, respiratory disease, psoriasis or rheumatoid arthritis (especially rheumatoid arthritis). [Respiratory disease is, for example, COPD, asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)} or rhinitis {acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}; and is particularly asthma or rhinitis].

In another aspect the present invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR5 receptor activity (especially rheumatoid arthritis)) in a warm blooded animal, such as man).

The invention also provides a compound of the invention, or a pharmaceutically acceptable salt thereof or a solvate thereof, for use as a medicament, especially a medicament for the treatment of rheumatoid arthritis.

In another aspect the present invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR5 receptor activity (especially rheumatoid arthritis)) in a warm blooded animal, such as man).

The invention further provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic

bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung or idiopathic interstitial pneumonia;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, Sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle;

in a warm blooded animal, such as man.

The present invention further provides a method of treating a chemokine mediated disease state (especially a CCR5 mediated disease state) in a warm blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a warm blooded animal, such as man, in particular modulating chemokine receptor (for example CCR5 receptor) activity, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the invention, or a pharmaceutically acceptable salt thereof or a solvate thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier. In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, aerosols, dry powder formulations, tablets, capsules, syrups, powders, granules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of $0.01 mgkg^{-1}$ to $100 mgkg^{-1}$ of the compound, preferably in the range of $0.1 mgkg^{-1}$ to $20 mgkg^{-1}$ of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a

period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of the invention, or a pharmaceutically acceptable salt thereof or a solvent thereof (hereafter Compound X), for therapeutic or prophylactic use in humans:

(a)

Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.0

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β-cyclodextrin may be used to aid formulation.

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

The invention will now be illustrated by the following non-limiting Examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography unless otherwise stated means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a "Bond Elut" column is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI". Where an "Isolute™ SCX column" is referred to, this means a column containing benzenesulphonic acid (non-endcapped) obtained from International Sorbent Technology Ltd.,

1st House, Duffryn Industial Estate, Ystrad Mynach, Hengoed, Mid Glamorgan, UK. Where "Argonaut™ PS-*tris*-amine scavenger resin" is referred to, this means a *tris*-(2-aminoethyl)amine polystyrene resin obtained from Argonaut Technologies Inc., 887 Industrial Road, Suite G, San Carlos, California, USA.

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields, when given, are for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio DMSO (CD_3SOCD_3) as the solvent unless otherwise stated; coupling constants (J) are given in Hz;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in percentage by volume;

(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (APCI) mode using a direct exposure probe; where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(x) LCMS characterisation was performed using a pair of Gilson 306 pumps with Gilson 233 XL sampler and Waters ZMD4000 mass spectrometer. The LC comprised water symmetry 4.6x50 column C18 with 5 micron particle size. The eluents were: A, water with 0.05% formic acid and B, acetonitrile with 0.05% formic acid. The eluent gradient went from 95% A to 95% B in 6 minutes. Where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$ and

(xi) the following abbreviations are used:

DMSO	dimethyl sulfoxide;
DMF	*N*-dimethylformamide;
DCM	dichloromethane;
THF	tetrahydrofuran;
DIPEA	*N*,*N*-diisopropylethylamine;

NMP	*N*-methylpyrrolidinone;
HATU	O-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate;
HBTU	O-(7-Benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate;
Boc	tert-butoxycarbonyl
MeOH	methanol;
EtOH	ethanol; and
EtOAc	ethyl acetate.

EXAMPLE 1

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[4-phenylphenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 25 of Table I).

To a mixture of *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (Method A; 500mg, 1.54mmol) and 3-phenyl-3-(4-phenylphenyl)propionaldehyde (Method B; 449mg, 1.54mmol) in DCM (10mL) and ethanol (2mL) was added one drop of acetic acid and the resulting mixture stirred at room temperature for 10min. Sodium triacetoxyborohydride (327mg, 1.54mmol) was added and the resulting mixture was stirred at room temperature for 2h. The reaction mixture was washed with 2M aqueous sodium hydroxide (2 x 10mL) and eluted through a 10g SCX cartridge with DCM (2 x 10mL), methanol (2 x 10mL) and finally 0.5M ammonia in methanol (3 x 10mL) to yield crude product which was purified by silica gel chromatography (eluent: DCM then ethyl acetate then 10% methanol in ethyl acetate) to yield the title compound (406mg); NMR: 0.95-1.3 (m, 3H) 1.3-1.95 (m, 8H) 2.2 (m, 3H) 2.8 (m, 2 H) 3.15 (s, 3H) 3.8 (m, 2H) 4.05 (m, 3H) 7.05-7.6 (m, 16H) 7.8 (d, 2H); MS: 595.

The procedure described in Example 1 can be repeated using different aldehydes (such as 3-phenyl-3-(pyridin-2-yl)propionaldehyde (Method G), 3-(4-chlorophenyl)-3-(3-fluorophenyl)propionaldehyde (Method I), (*S*)-3-phenyl-3-(4-methanesulfonylphenyl)propionaldehyde (Method N), (*R*)-3-(3-fluorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye (Method O), (*S*)-3-(4-fluorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye (Method P), (*R*)-3-(3-chlorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye (Method Q), (*R*)-3-(3,4-difluorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye (Method R), (*S*)-3-(4-methoxyphenyl)-3-(4-

methanesulfonylphenyl)propionaldehdye (Method S), or (*R*)-3-(3,5-difluorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye (Method T)) in place of 3-phenyl-3-(4-phenylphenyl)propionaldehyde.

EXAMPLE 2

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[4-methoxycarbonyl-phenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 4 of Table I).

This was prepared from 3-phenyl-3-(4-methoxycarbonylphenyl)propionaldehyde (Method F) and *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide using a method similar to that used to prepare *N*-[1-(3-phenyl-3-[4-phenylphenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Example 1). NMR ($CDCl_3$): 1.1 and 1.2 (t, 3H), 1.5 (m, 1H), 1.8 (m, 2H), 2.0 (br t, 2H), 2.2 (m, 4H), 2.9 (m, 2H), 3.0 (s, 3H), 3.3 (m, 2H), 3.8 (m, 2H), 3.9 (s, 3H), 4.1 (m, 2H), 4.4 (m, 1H), 7.2 (m, 7H), 7.5 (m, 2H) and 7.9 (m, 4H); MS: 577.

EXAMPLE 3

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[4-{morpholin-4-ylcarbonyl}phenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 5 of Table I).

To a solution of *N*-[1-(3-phenyl-3-[4-carboxyphenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (Method H; 100mg, 0.16mmol) in DCM (4mL) was added oxalyl chloride (0.05mL) and the resulting mixture was stirred at room temperature for 3h. The mixture was cooled to 0°C and a solution of morpholine in DCM was added dropwise until a pH of 9 was achieved. The reaction mixture was washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel chromatography (eluent: 2% ammonia/10% methanol in DCM) giving the title compound (34mg); NMR ($CDCl_3$): 1.1 and 1.2 (t, 3H), 1.4 (m, 1H), 1.6 (m, 2H), 1.8 (m, 2H), 2.0 (m, 2H), 2.2 (m, 4H), 2.9 (m, 2H), 3.0 (s, 3H), 3.3 (q, 2H), 3.6 (br m, 7H), 3.8 (m, 2H), 4.0 (m, 1H), 4.4 (m, 1H), 7.2 (m, 9H), 7.5 (m, 2H) and 7.9 (d, 2H); MS: 632.

EXAMPLE 4

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[4-carboxamidophenyl]-propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 6 of Table I).

To a solution of *N*-[1-(3-phenyl-3-[4-carboxyphenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (150mg, 0.25mmol) in DCM (4mL) was added oxalyl chloride (0.022mL, 0.25mmol) and the resulting mixture was stirred at room temperature for 18h. A solution of ammonia in methanol (10mL) was added and the resulting mixture was stirred at room temperature for 2h. The reaction mixture was washed with water and evaporated. The residue was purified by silica gel chromatography (eluent: 1% ammonia/10% methanol in DCM) giving the title compound (23mg); NMR ($CDCl_3$): 1.1 and 1.2 (t, 3H), 1.5 (m, 2H), 1.6 (m, 1H), 1.8 (m, 2H), 2.0 (m, 2H), 2.2 (m, 4H), 2.9 (m, 2H), 3.0 (s, 3H), 3.3 (q, 2H), 3.8 (m, 2H), 4.0 (m, 2H), 4.4 (m, 1H), 7.2 (m, 7H), 7.4 (m, 2H), 7.7 (m, 2H) and 7.9 (d, 2H); MS: 562.

EXAMPLE 5

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[4-isopropoxycarbonyl-phenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (Compound No. 7 of Table I).

To a suspension of *N*-[1-(3-phenyl-3-[4-carboxyphenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (40mg, 0.07mmol) in 2-propanol (4mL) was added thionyl chloride (3 drops). The resulting mixture was heated to reflux for 18h, allowed to cool and evaporated. The residue was triturated with diethyl ether to give the title compound (31mg); NMR: 1.0 and 1.1 (t, 3H), 1.3 (t, 3H), 1.7 (m, 2H), 2.2 (m, 2H), 2.8 (m, 2H), 3.0 (m, 2H), 3.2 (s, 3H), 3.3 (m, 4H), 3.5 (m, 2H), 3.8 (m, 2H), 4.0 and 4.2 (m, 1H), 4.1 (m, 1H), 7.2 (m, 5H), 7.5 (br d, 4H) and 7.8 (br t, 4H); MS: 605.

EXAMPLE 6

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[4-cyanophenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 3 of Table I).

To a mixture of *N*-[1-(3-phenyl-3-[4-carboxamidophenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Example 4; 0.33mmol) in dioxane (5mL) and pyridine (0.05mL, 0.6mmol) at 0°C was added trifluoroacetic anhydride (0.1mL, 0.66mmol)

and the resulting mixture stirred at room temperature for 1h. The reaction mixture was washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was purified by eluting through an SCX cartridge with methanol then 2M ammonia in methanol to yield the title compound (27mg); NMR ($CDCl_3$): 1.1 and 1.3 (t, 3H), 1.5 (m, 1H), 1.7 (m, 2H), 1.8 (m, 2H), 2.0 (m, 1H), 2.2 (m, 4H), 2.9 (m, 2H), 3.0 (s, 3H), 3.3 (q, 2H), 3.8 (m, 2H), 4.0 (m, 1H), 4.4 (m, 1H), 7.2 (m, 7H), 7.4 (m, 2H), 7.6 (m, 2H) and 7.9 (d, 2H); MS: 544.

EXAMPLE 7

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[4-aminophenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 9 of Table I).

N-[1-(3-Phenyl-3-[4-Boc-aminophenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Example 8; 6g, 9.5mmol) was dissolved in trifluoroacetic acid (25mL) and the resulting mixture was stirred at room temperature for 2h. The mixture was evaporated and the residue dissolved in 2M aqueous sodium hydroxide (50mL) and DCM (50mL). The aqueous phase was extracted with DCM (3 x 25mL) and the combined organic phases dried ($MgSO_4$) then eluted through a 50g SCX cartridge with DCM (3 x 25mL), methanol (3 x 25mL) and 1M ammonia in methanol (5 x 25mL) to give the title compound (4.5g); MS: 534.

EXAMPLE 8

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[4-Boc-aminophenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 10 of Table I).

This was prepared from 3-phenyl-3-(4-Boc-aminophenyl)propionaldehyde (Method C) and *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide using a method similar to that used to prepare *N*-[1-(3-phenyl-3-[4-phenylphenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Example 1).

EXAMPLE 9

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[4-pyridin-2-ylacetylamino phenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 11 of Table I).

To a solution of 2-pyridylacetic acid hydrochloride (81mg, 4.7mmol) in DCM (10mL) was added triethylamine (47mg, 4.7mmol) and carbonyl diimidazole (75mg, 4.7mmol). The resulting mixture was stirred at room temperature for 4h. *N*-[1-(3-Phenyl-3-[4-aminophenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (250mg, 4.7mmol) was added and the resulting mixture was stirred at room temperature for 18h. Isocyanate scavenger resin (0.3g) was added and the resulting mixture was stirred at room temperature for 2h before filtration and washing with 2M aqueous sodium hydroxide (10mL). The filtrate was extracted with DCM and extracts dried and evaporated to give the title compound (184mg); MS: 653.

The procedure described in Example 9 can be repeated using different carboxylic acids (such as 3-pyridylacetic acid hydrochloride or 4-pyridylacetic acid hydrochloride) in place of 2-pyridylacetic acid hydrochloride.

EXAMPLE 10

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[4-phenylacetylamino phenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 14 of Table I).

To a mixture of *N*-[1-(3-phenyl-3-[4-aminophenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (250mg, 4.7mmol) and triethylamine (47mg, 4.7mmol) in DCM (10mL) was added phenylacetyl chloride (72mg, 4.7mmol) and the resulting mixture was stirred at room temperature for 18h. Trisamine scavenger resin (100mg) was added and the resulting mixture was stirred at room temperature for 2h before filtration. The filtrate was washed with saturated aqueous sodium bicarbonate solution (10mL), dried and eluted through a 10g SCX cartridge with DCM (4 x 10mL), methanol (4 x 10mL) and 1M ammonia in methanol (4 x 10mL) to give the title compound (202mg); MS: 652.

The procedure described in Example 10 can be repeated using different carbonyl chlorides (such as benzoyl chloride, 4-chlorobenzoyl chloride or pivaloyl chloride) or sulfonyl

chlorides (such as benzene sulfonyl chloride or methane sulfonyl chloride) or isocyanates (such as phenyl isocyanate or cyclohexyl isocyanate) in place of phenylacetic acid, and different anilines (such as *N*-[1-(3-[3-fluorophenyl]-3-[4-aminophenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide) (Example 12) in place of *N*-[1-(3-phenyl-3-[4-aminophenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide. When isocyanates are employed the triethylamine is omitted from the reaction.

EXAMPLE 11

This Example illustrates the preparation of (2*R*)-*N*-[1-(4-[4-chlorophenyl]-4-[3-fluorophenyl]but-2-yl)piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 27 of Table I).

To a mixture of (2*R*)-1-(4-[4-chlorophenyl]-4-[3-fluorophenyl]but-2-yl)-4-ethylaminopiperidine (Method K; 0.22g, 0.56mmol) and 4-methanesulfonylphenylacetic acid (0.33g, 0.62mmol) in DCM (10mL) was added diisopropylcarbodiimide (0.1mL, 0.62mmol) and the resulting mixture was stirred at room temperature for 18h before evaporation. The crude product was purified by eluting through a Bond Elut with DCM then 1% ammonia/10% methanol in DCM to give the title compound as a solid (0.36g); NMR ($CDCl_3$): 0.9 (d, 3H), 1.2 (t, 3H), 1.5 (m, 1H), 1.6 (m, 2H), 1.8 (m, 1H), 2.0 (m, 1H), 2.2 (m, 2H), 2.4 (m, 1H), 2.5 (m, 1H), 2.7 (m, 1H), 3.0 (s, 3H), 3.3 (m, 2H), 3.8 (m, 2H), 3.9 and 4.3 (m, 1H), 4.2 (m, 1H), 4.4 (m, 1H), 6.9 (m, 3H), 7.2 (m, 5H), 7.5 (m, 2H) and 7.9 (d, 2H); MS: 585.

EXAMPLE 12

This Example illustrates the preparation of *N*-[1-(3-[3-fluorophenyl]-3-[4-aminophenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (Compound No. 44 of Table I).

This was prepared from *N*-[1-(3-[3-fluorophenyl]-3-[4-Boc-aminophenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Example 13) using a method similar to that used to prepare *N*-[1-(3-phenyl-3-[4-aminophenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Example 7); NMR: 1.0 and 1.15 (t, 3H), 1.7 (m, 2H), 2.3 (m, 2H), 2.8 (m, 2H), 2.5 (m, 2H), 3.0 (m, 2H), 3.2 (s, 3H), 3.2 and 3.3 (m, 2H), 3.5 (m, 2H), 3.7 and 4.1 (m, 1H), 3.8 and 3.9 (s, 2H), 4.35 (m, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.35 (m, 3H), 7.45 (m, 4H), 7.8 (d, 2H); MS: 552 (MH+).

EXAMPLE 13

This Example illustrates the preparation of *N*-[1-(3-[3-fluorophenyl]-3-[4-Boc-aminophenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 43 of Table I).

This was prepared from 3-(3-fluorophenyl)-3-(4-Boc-aminophenyl)propionaldehyde (Method L) and *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide using a method similar to that used to prepare *N*-[1-(3-phenyl-3-[4-phenylphenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Example 1); NMR ($CDCl_3$): 1.15 and 1.25 (t, 3H), 1.5 (s, 9H), 1.5 and 1.65 (m, 2H), 1.95 (m, 2H), 2.0-2.3 (m, 6H), 2.9 and 3.0 (m, 2H), 3.0 (s, 3H), 3.35 (ABq, 2H), 3.5 and 3.9 (m, 1H), 3.8 and 3.9 (s, 2H), 4.4 (m, 1H), 6.55 (br s, 1H), 6.8-7.0 (m, 4H), 7.1-7.3 (m, 4H), 7.5 (m, 2H), 7.9 (d, 2H); MS: 652 (MH+).

EXAMPLE 14

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[4-methanethiophenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 41 of Table I).

This was prepared from 3-phenyl-3-(4-methanethiophenyl)propionaldehyde (Method M) and *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide using a method similar to that used to prepare *N*-[1-(3-phenyl-3-[4-phenylphenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Example 1); NMR ($CDCl_3$): 1.15 and 1.25 (t, 3H), 1.5 and 1.65 (m, 2H), 1.95 (m, 2H), 2.1-2.4 (m, 6H), 2.4 (s, 3H), 2.95 and 3.1 (m, 2H), 3.0 (s, 3H), 3.35 (ABq, 2H), 3.5 and 3.9 (m, 1H), 3.8 and 3.9 (s, 2H), 4.4 (m, 1H), 7.2 (m, 9H), 7.4 (m, 2H), 7.85 (d, 2H); MS: 565 (MH+).

EXAMPLE 15

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[4-methanesulfonylphenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 40 of Table I).

To a stirred solution of *N*-[1-(3-phenyl-3-[4-methanethiophenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Example 14, 0.33g, 0.58mmol) in DCM (50mL) was added 3-chloroperbenzoic acid (0.5g, 2.92mmol) and the resulting mixture was stirred at room temperature for 2h. The mixture was washed with water, dried ($MgSO_4$), pre-absorbed onto a Bond Elut, and eluted with a gradient of DCM to 1% ammonia/10% methanol

in DCM giving a white foam (0.205g); MS: 613. This was dissolved in DCM (5mL) and the solution cooled to 0°C. To this solution was added a mixture prepared as follows: formic acid (0.03mL, 0.75mmol) was dropwise to acetic anhydride (0.06mL, 0.625mmol) and the resulting mixture heated to 55°C for 2h then cooled. The resulting mixture was stirred at room temperature for 48h. Water was added and the mixture basified with potassium carbonate to pH of approximately 10. The organic phase was dried ($MgSO_4$), pre-absorbed onto a Bond Elut and eluted with a gradient of DCM to 1% ammonia/10% methanol in DCM giving the title compound (0.12g); NMR ($CDCl_3$): 1.15 and 1.25 (t, 3H), 1.5 and 1.65 (m, 2H), 1.6-2.0 (m, 4H), 2.25 (m, 4H), 2.9 and 3.0 (m, 2H), 3.0 (s, 3H), 3.05 (s, 3H), 3.35 (ABq, 2H), 3.5 and 3.8 (m, 1H), 3.8 and 4.1 (s, 2H), 4.4 (m, 1H), 7.2 (m, 5H), 7.45 (m, 4H), 7.8 (d, 2H), 7.9 (d, 2H); MS: 597 (MH+).

Below is presented certain NMR data for some compounds of the invention.

(*S*)-*N*-[1-{3-phenyl-3-(4-methanesulfonylphenyl)propyl}-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 50 of Table I).

NMR ($CDCl_3$): 1.15 and 1.25 (t, 3H), 1.5 and 1.65 (m, 2H), 1.6-2.0 (m, 4H), 2.25 (m, 4H), 2.9 and 3.0 (m, 2H), 3.0 (s, 3H), 3.05 (s, 3H), 3.35 (ABq, 2H), 3.5 and 3.8 (m, 1H), 3.8 and 4.1 (s, 2H), 4.4 (m, 1H), 7.2 (m, 5H), 7.45 (m, 4H), 7.8 (d, 2H), 7.9 (d, 2H)

(*S*)-*N*-[1-{3-(4-fluorophenyl)-3-(4-methanesulfonylphenyl)propyl}-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (Compound No. 52 of Table I).

NMR (d6-DMSO, 120°C): 1.13 (t, 3H), 1.65 (m, 1H), 1.75 (m, 2H), 2.40 (m, 1H), 2.61 (m, 2H), 2.9-3.1 (m, 4H), 3.14 (s, 6H), 3.3-3.4 (m, 4H), 3.83 (s, 2H), 4.15 (m, 1H), 4.25 (dd, 1H), 7.10 (dd, 2H), 7.32 (dd, 2H), 7.40 (d, 2H), 7.50 (d, 2H), 7.85 (m, 4H), 11.1 (br s, 1H).

(*R*)-*N*-[1-{3-(3-chlorophenyl)-3-(4-methanesulfonylphenyl)propyl}-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (Compound No. 53 of Table I).

NMR (d6-DMSO, 120°C): 1.13 (t, 3H), 1.65 (m, 1H), 1.75 (m, 2H), 2.40 (m, 1H), 2.61 (m, 2H), 2.9-3.1 (m, 4H), 3.14 (s, 3H), 3.3-3.4 (m, 7H), 3.83 (s, 2H), 4.20 (m, 1H), 4.30 (dd, 1H), 7.25 (m, 1H), 7.32 (m, 2H), 7.40 (s, 1H), 7.50 (d, 2H), 7.60 (d, 2H), 7.85 (m, 4H), 11.3 (br s, 1H).

(*R*)-*N*-[1-{3-(3,4-difluorophenyl)-3-(4-methanesulfonylphenyl)propyl}-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (Compound No. 54 of Table I).

NMR (d6-DMSO, 120°C): 1.13 (t, 3H), 1.65 (m, 1H), 1.75 (m, 2H), 2.40 (m, 1H), 2.61 (m, 2H), 2.9-3.1 (m, 4H), 3.14 (s, 6H), 3.3-3.4 (m, 4H), 3.90 (s, 2H), 4.25 (m, 1H), 4.35 (dd, 1H), 7.25 (m, 1H), 7.32 (dd, 1H), 7.45 (dd, 1H), 7.52 (d, 2H), 7.63 (d, 2H), 7.85 (m, 4H), 11.3 (br s, 1H).

(*R*)-*N*-[1-{3-(3,5-difluorophenyl)-3-(4-methanesulfonylphenyl)propyl}-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (Compound No. 56 of Table I).

NMR (d6-DMSO, 120°C): 1.13 (t, 3H), 1.35 (m, 2H), 1.75 (m, 2H), 2.40 (m, 2H), 2.61 (m, 2H), 2.9-3.1 (m, 4H), 3.14 (s, 6H), 3.35 (q, 2H), 3.45 (m, 2H), 3.87 (s, 2H), 4.15 (m, 1H), 4.35 (dd, 1H), 6.95 (t, 1H), 7.10 (d, 2H), 7.50 (d, 2H), 7.63 (d, 2H), 7.85 (m, 4H), 11.2 (br s, 1H).

Method A

N-(4-Piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide

Step 1: Preparation of 1-phenylmethyl-4-ethylaminopiperidine dihydrochloride

To a solution of 1-phenylmethyl-4-piperidone (25.0g, 132mmol) in THF (250mL) was added ethylamine hydrochloride (12.0g, 147 mol) and methanol (50mL) and the resulting mixture stirred at room temperature for 10min. Sodium triacetoxyborohydride (40g, 189mmol) was added portionwise and the resulting mixture stirred at room temperature for 1h. 2M Sodium hydroxide solution (250mL) was added and the resulting mixture extracted with diethyl ether. The organic extracts were dried (K_2CO_3) and evaporated to give 1-phenylmethyl-4-ethylaminopiperidine as an oil. This was dissolved in ethanol (500mL) and concentrated hydrochloric acid (20mL) was added. The resulting crystals were collected, washed with diethyl ether and dried giving the sub-titled compound as a solid (38 g); NMR: ($CDCl_3$): 1.10 (t, 3H), 1.40 (m, 2H), 1.83 (m, 2H), 2.02 (m, 2H), 2.65 (q, 2H), 2.85 (m, 2H), 3.50 (s, 2H), 3.75 (m, 1H), 7.2 - 7.4 (m, 5H); MS: 219 (MH+).

Step 2: Preparation of *N*-(1-Phenylmethyl-4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide

To a solution of 1-phenylmethyl-4-ethylaminopiperidine dihydrochloride (32.0g, 110mmol) in DCM (500mL) was added *N,N*-diisopropylethylamine (60mL) with stirring to ensure complete dissolution. 4-Methanesulfonylphenylacetic acid (25.0g, 117mmol), 4-Dimethylaminopyridine (2.0g) and dicyclohexylcarbodiimide (25.0g, 121mmol) were added and the resulting mixture was stirred at room temperature for 20h. The precipitate was removed by filtration and the resulting solution was washed successively with 2N aqueous HCl, water and 1N aqueous NaOH, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel chromatography (eluent: 10% MeOH/ethyl acetate) to afford the sub-titled compound (35g, 76%); NMR: 1.00 and 1.14 (t, 3H), 1.45 and 1.70 (m, 2H), 1.95 (br m, 2H), 2.80 (br m, 2H), 3.18 (s, 3H), 3.20 and 3.33 (q, 2H), 3.45 (s, 2H), 3.80 and 3.87 (s, 2H), 3.70 and 4.10 (m, 1H), 7.2 - 7.3 (m, 5H), 7.48 (m, 2H), 7.82 (m, 2H); MS: 415 (MH+).

Step 3: Preparation of the title compound

To a solution of *N*-(1-phenylmethyl-4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenyl-acetamide (34g, 82mmol) in ethanol (600mL) was added ammonium formate (40g). The mixture was purged with argon and 30% Pd on carbon (4.2g) was added. The resulting mixture was stirred at reflux for 4h, then allowed to cool and filtered through diatomaceous earth. The filtrate was evaporated to give a thick oil which solidified on standing to yield the title compound (24.9g, 94%); NMR: 1.02 and 1.15 (t, 3H), 1.4 -1.6 (br m, 4H), 2.45 (m, 2H), 2.93 (br m, 2H), 3.18 (s, 3H), 3.20 and 3.32 (q, 2H), 3.72 and 4.18 (m, 1H), 3.80 and 3.87 (s, 2H), 7.50 (m, 2H), 7.85 (m, 2H); MS: 325 (MH+).

Method B

3-Phenyl-3-(4-phenylphenyl)propionaldehyde

Step 1: Preparation of ethyl 3-phenyl-3-(4-phenylphenyl)acrylate

To a solution of triethylphosphonoacetate (6.7g, 26mmol) in THF (100mL) at 0°C was added lithium bis(trimethylsilyl)amide (26mL, 1M, 26mmol). The resulting mixture was stirred at 0°C for 20min. 4-Benzoylbiphenyl (6.5g, 26mmol) was added and the resulting mixture was stirred at room temperature for 48h. The mixture was evaporated and the residue dissolved in ethyl acetate (200mL). The solution was washed with 2M hydrochloric acid (2 x 100mL), dried and evaporated giving the sub-titled compound (11g).

Step 2: Preparation of ethyl 3-phenyl-3-(4-phenylphenyl)propionoate

Ethyl 3-phenyl-3-(4-phenylphenyl)acrylate (11g) was dissolved in ethanol (200mL) and the solution purged with argon. 20% Palladium hydroxide (2g) was added and the resulting mixture was stirred at room temperature under an atmosphere of hydrogen (balloon) for 72h. The mixture was purged with argon, filtered and the filtrate evaporated. The crude product was purified by silica gel chromatography (eluent: isohexane then 25% ethyl acetate in isohexane) to give the sub-titled compound (2.8g).

Step 3: Preparation of 3-phenyl-3-(4-phenylphenyl)propan-1-ol

To a solution of ethyl 3-phenyl-3-(4-phenylphenyl)propionoate (2.8g, 8.48mmol) in THF (30mL) was added lithium aluminium hydride (8.48mL, 1M, 8.48mmol) dropwise over 30min. The resulting mixture was stirred at 0°C for 1h. 2M Aqueous sodium hydroxide (8mL) was added dropwise. The mixture was filtered through Celite®, washing with ethyl acetate (3 x 25mL). The filtrate and washings were combined and evaporated. The residue was dissolved in ethyl acetate (50mL) and the resulting solution washed with water (50mL) and 2M hydrochloric acid (2 x 50mL), dried and evaporated. The residue was purified by silica gel chromatography (eluent: isohexane then 40% ethyl acetate in isohexane) to give the sub-titled compound (1.3g); NMR: 2.2 (q, 2H) 3.3 (q, 2H) 4.1 (t, 1H) 4.25 (t,1H) 7.1-7.6 (m, 14H).

Step 4: Preparation of the title compound

To a solution of 3-phenyl-3-(4-phenylphenyl)propan-1-ol (1.3g, 3.3mmol) in DCM (50mL) was added Dess-Martin periodinane (1.8g, 4.4mmol) and the resulting mixture was stirred at room temperature for 1.5h. The mixture was washed with 2M aqueous sodium hydroxide (2 x 20mL), dried and evaporated to give the title compound (1.3g); NMR: 3.2 (d, 2 H) 4.6 (t, 1H) 7.1-7.7 (m, 14H) 9.7 (s, 1H).

Method C

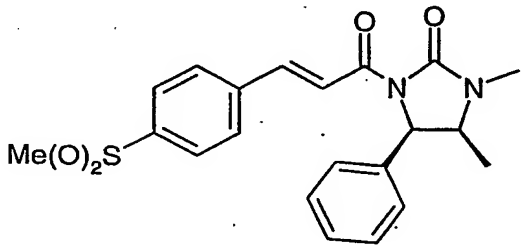
3-Phenyl-3-(4-Boc-aminophenyl)propionaldehyde

This was prepared from 4-nitrobenzophenone using a similar sequence of reactions to that used to prepare 3-phenyl-3-(4-phenylphenyl)propanionaldehyde from 4-benzoylbiphenyl (Method B), except that an additional step was included between Steps 2 and 3, namely

treatment of ethyl 3-phenyl-3-(4-aminophenyl)propionate with di-tert-butyldicarbonate to form ethyl 3-phenyl-3-(4-Boc-aminophenyl)propionate.

Method D

E-(4*R*, 5*S*)-1-(3-[4-Methanesulfonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one



To a stirred solution of 3-(4-methanesulfonylphenyl)acrylic acid (7.14g, 31.5mmol) in DCM (10mL) was added thionyl chloride (3mL, 34.7mmol) dropwise and the resulting mixture was stirred at room temperature for 18h. To this solution was added DIPEA (5.04mL, 28.9mmol) dropwise at room temperature. The resulting solution was added to a stirred solution of (4*R*, 5*S*)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (5.0g, 26.3mmol) in DCM (20mL) and DIPEA (4.58mL, 26.9mmol) and the resulting mixture stirred at room temperature for 4h. The mixture was washed with water and brine, pre-absorbed onto a Bond Elut and eluted with a gradient of isohexane to ethyl acetate giving the title compound as a solid (7.61g, 73%); NMR ($CDCl_3$): 0.84 (d, 3H), 2.89 (s, 3H), 3.04 (s, 3H), 3.98 (m, 1H), 5.42 (d, 1H), 7.20 (m, 2H), 7.32 (m, 3H), 7.69 (d, 1H), 7.74 (d, 2H), 7.93 (d, 2H), 8.31 (d, 1H); MS: 399 (MH+).

Method E

4-Methanethiobenzophenone

Step 1: Preparation of 1-(4-methanethiophenyl)phenylmethanol

To a solution of 4-methanethiobenzaldehyde (21g, 138mmol) in THF (200mL) at 0°C was added phenyl lithium (84mL, 152mmol) dropwise. The resulting mixture was stirred for 18h with warming to room temperature. The mixture was washed with saturated aqueous ammonium chloride and brine, dried ($MgSO_4$) and evaporated giving the sub-titled compound as a solid (30.16g, 95%); NMR ($CDCl_3$): 2.28 (dt, 2H), 2.43 (s, 3H), 3.58 (t, 2H), 4.10 (t, 1H), 7.23 (m, 5H).

Step 2: Preparation of title compound

To a solution of 1-(4-methanethiophenyl)phenylmethanol (30g, 130mmol) in DCM (400mL) was added Dess-Martin periodinane (55g, 143mmol) portionwise at room temperature. The resulting mixture was stirred at room temperature for 1h, washed with 2M aqueous sodium hydroxide, dried ($MgSO_4$), pre-absorbed onto a silica column and eluted with a gradient elution (isohexane to DCM) to give the title compound as a solid (18.57g, 63%); NMR ($CDCl_3$): 2.53 (s, 3H), 7.29 (m, 2H), 7.48 (m, 2H), 7.58 (m, 1H), 7.76 (m, 4H); MS: 229 (MH+).

Method F

3-Phenyl-3-(4-methoxycarbonylphenyl)propionaldehyde ……

Step 1: Preparation of diphenylmethane-4-carboxylic acid methyl ester

To a suspension of diphenylmethane-4-carboxylic acid (10g, 47mmol) in methanol (50mL) was added thionyl chloride (0.34mL, 4.7mmol) dropwise. The resulting mixture was heated to reflux for 3h then allowed to cool. The mixture was evaporated and eluted through a plug of silica gel to give the sub-titled compound (9.7g, 91%); NMR ($CDCl_3$): 3.9 (s, 3H), 4.0 (s, 2H), 7.2 (m, 7H) and 8.0 (d, 2H).

Step 2: Preparation of 3-phenyl-3-(4-methoxycarbonylphenyl)but-1-ene

To a solution of diphenylmethane-4-carboxylic acid methyl ester (9.7g, 43mmol) in THF (100mL) under argon at –78°C was added lithium diisopropylamide (23.5mL, 2M, 47mmol) dropwise and the resulting mixture was stirred at –78°C for 1h. Allyl bromide (1.85mL, 21mmol) was added and the resulting mixture was allowed to warm to room temperature over 18h. The reaction mixture was washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel chromatography (eluent: DCM) to give the sub-titled compound as an oil (4.3g); NMR ($CDCl_3$): 2.87 (dd, 2H), 3.91 (s, 3H), 4.12 (t, 1H), 5.03 (m, 2H), 5.76 (m, 1H), 7.24 (m, 7H), 8.01 (d, 2H).

Step 3: Preparation of the title compound

A solution of 3-phenyl-3-(4-methoxycarbonylphenyl)but-1-ene (3.26g, 12.2mmol) in methanol (100mL) was purged with oxygen gas at –78°C for 10min. Ozone was bubbled through for 1h until a blue colour persisted. Dimethyl sulfide (1.8mL, 25mmol) was added

and the resulting mixture was stirred at room temperature for 1h then evaporated to give the title compound which was used in the next reaction without further purification.

Method G

3-Phenyl-3-(pyridin-2-yl)propionaldehyde

This was prepared from 2-benzylpyridine using a similar method to that used to prepare 3-phenyl-3-(4-methoxycarbonylphenyl)propionaldehyde from diphenylmethane-4-carboxylic acid methyl ester (Method F).

Method H

N-[1-(3-phenyl-3-[4-carboxyphenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride

To a solution of *N*-[1-(3-phenyl-3-[4-methoxycarbonylphenyl]propyl)-piperidin-4-yl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Example 2; 2.36g, 4.1mmol) in methanol (40mL) was added sodium hydroxide (1.64g, 41mmol) and the resulting mixture was stirred at room temperature for 3 days. The mixture was evaporated, the residue was taken up in water and acidified to pH 1. The solid was collected and triturated with methanol to give the title compound (0.73g); NMR: 1.0 and 1.1 (t, 3H), 1.4 (m, 2H), 1.6 (m, 2H), 1.8 (br t, 2H), 2.2 (m, 4H), 2.8 (br t, 2H), 3.2 (s, 3H), 3.3 (m, 1H), 3.6 (m, 1H), 3.8 (d, 2H), 4.0 (m, 2H), 7.1 (m, 1H), 7.3 (m, 4H), 7.5 (m, 4H) and 7.8 (d, 4H); MS: 563.

Method I

3-(4-Chlorophenyl)-3-(3-fluorophenyl)propionaldehyde

This was prepared from 4-chloro-3'-fluorobenzophenone (Method N) using a similar sequence of reactions to that used to prepare 3-phenyl-3-(4-phenylphenyl)propanionaldehyde from 4-benzoylbiphenyl (Method B), except that Step 2 was omitted.

Method J

4-Chloro-3'-fluorobenzophenone

Step 1: Preparation of 4-chlorophenyl-3-fluorophenylmethanol

To a solution of 3-fluorobenzaldehyde (5g, 40mmol) in THF (20mL) was added 4-chlorophenylmagnesium bromide (44mL, 1M in diethyl ether, 44mmol) dropwise and the resulting mixture was stirred at room temperature for 1h. 2M Hydrochloric acid (10mL) was

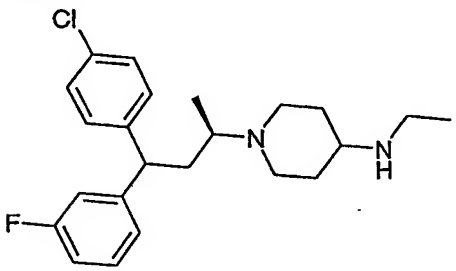
added portionwise, the layers separated and the organic phase evaporated. The residue was purified by Bond Elut chromatography (eluent: isohexane then DCM) to give the sub-titled compound (5.1g, 48%); NMR ($CDCl_3$): 2.2 (d, 1H), 5.8 (d, 1H), 7.0 (m, 1H), 7.1 (m, 2H) and 7.3 (m, 5H).

Step 2: Preparation of the title compound

To a solution of 4-chlorophenyl-3-fluorophenylmethanol (1.55g, 6.55mmol) in DCM (40mL) was added Dess-Martin periodinane (3.06g, 7.20mmol) and the resulting mixture was stirred at room temperature for 30min. The reaction mixture was washed with 2M aqueous sodium hydroxide, dried and evaporated. The residue was purified by Bond Elut chromatography (eluent: isohexane then DCM) to give the title compound as a white solid (1.00g, 64%); NMR ($CDCl_3$): 7.3 (m, 1H), 7.5 (m, 5H) and 7.8 (d, 2H).

Method K

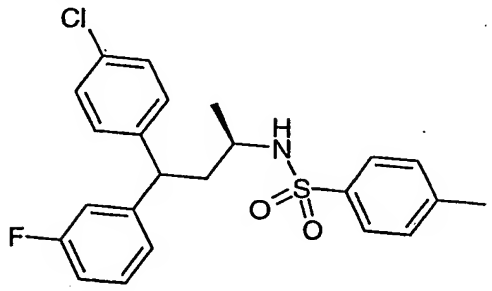
(2*R*)-1-(4-[4-Chlorophenyl]-4-[3-fluorophenyl]but-2-yl)-4-ethylaminopiperidine



Step 1: Preparation of 4-chloro-3'-fluorodiphenylmethane

To a mixture of 4-chlorophenyl-3-fluorophenylmethanol (Step1 of Method J; 10g, 38mmol) and glacial acetic acid (150mL) was added iodine (10g, 40mmol) and hypophosphoric acid (30mL, 50% aqueous, 285mmol). The resulting mixture was stirred at 60°C for 16h, allowed to cool and diluted with water (300mL). The mixture was extracted twice with isohexane and the combined extracts washed with saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel chromatography (eluent: isohexane) to give the sub-titled compound (7.5g); NMR ($CDCl_3$): 3.9 (s, 2H), 6.9 (m, 3H), 7.1 (d, 2H) and 7.2 (m, 3H); MS: 220 (MH+).

Step 2: Preparation of (1*R*)-*N*-tosyl-3-(4-chlorophenyl)-3-(3-fluorophenyl)-1-methylpropylamine



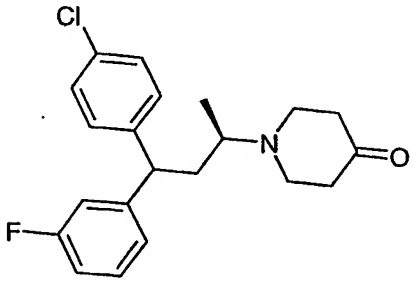
To a solution of 4-chloro-3'-fluorodiphenylmethane (7.0g, 32mmol) in THF (100mL) at –10°C was added lithium diisopropylamide (20mL, 2M in hexane/THF, 40mmol) and the resulting mixture was stirred at –10°C for 10min. during which time a deep red colour was observed. (*R*)-2-Methyl-1-tosylaziridine (prepared from *D*-alaninol in two steps using literature procedures*; 6.7g, 32mmol) was added and the resulting mixture was stirred with warming to room temperature for 1h. The reaction mixture was partitioned between saturated aqueous ammonium chloride and diethyl ether, the combined organic phases were dried ($MgSO_4$) and evaporated to give the sub-titled compound as a solid (12g); NMR ($CDCl_3$): 1.0 (dd, 3H), 2.0 (m, 1H), 2.1 (m, 1H), 2.4 (s, 3H), 3.1 (m, 1H), 4.0 (m, 1H), 4.6 (m, 1H), 6.8 (m, 1H), 6.9 (m, 1H), 7.2 (m, 8H) and 7.6 (m, 2H).

* Tetrahedron 44, 3919 (1988), Chem. Pharm. Bull. 25, 29 (1977).

Step 3: Preparation of (1*R*)-3-(4-chlorophenyl)-3-(3-fluorophenyl)-1-methylpropylamine

A mixture of (1*R*)-*N*-tosyl-3-(4-chlorophenyl)-3-(3-fluorophenyl)-1-methylpropylamine (10g, 23mmol) and 30% hydrobromic acid in glacial acetic acid (10mL) was heated to 80°C for 18h, allowed to cool and evaporated. The residue was partitioned between diethyl ether and 2M aqueous sodium hydroxide. The organic phase was evaporated and the residue purified by silica gel chromatography (eluent: 2:1 ethyl acetate/methanol) to give the sub-titled compound (2.2g); NMR ($CDCl_3$): 1.4 (d, 3H), 2.2 (m, 2H), 3.2 (br s, 2H), 4.3 (m, 1H) and 7.0 (br m, 8H): MS: 278 (MH+).

Step 4: Preparation of (2*R*)-1-(4-[4-chlorophenyl]-4-[3-fluorophenyl]but-2-yl)-4-piperidone



To a solution of (1*R*)-3-(4-chlorophenyl)-3-(3-fluorophenyl)-1-methylpropylamine (2.0g 7.2mmol) in ethanol (50mL) was added a solution of potassium carbonate (1.5g) in water (5mL) and the resulting mixture heated to reflux with stirring. A solution of 1-methyl-1-ethyl-4-oxopiperidinium iodide (2.5g, 9.3mmol) in water (15mL) was added dropwise. The resulting mixture was stirred at reflux for 10min. then allowed to cool. The mixture was concentrated to about half the volume then extracted with DCM. The combined extracts were evaporated and the residue purified by silica gel chromatography (eluent: ethyl acetate) to give the sub-titled compound (700mg); NMR: 0.9 (m, 3H), 2.0 (m, 1H), 2.2 (m, 1H), 2.3 (m, 4H), 2.4 (m, 5H), 2.7 (m, 2H), 7.0 (m, 1H), 7.2 (m, 2H) and 7.3 (m, 5H).

Step 5: Preparation of the title compound

To a solution of (2*R*)-1-(4-[4-chlorophenyl]-4-[3-fluorophenyl]but-2-yl)-4-piperidone (400mg, 1.1mmol) in ethanol (20mL) was added ethylamine hydrochloride (200mg, 2.5mmol) and the resulting mixture was stirred at room temperature for 10min. until dissolved. Sodium triacetoxyborohydride (400mg, 1.88mmol) was added and the resulting mixture was stirred at room temperature for 18h. The reaction mixture was partitioned between 2M aqueous sodium hydroxide and diethyl ether. The organic phase was dried and evaporated and the residue purified by silica gel chromatography (eluent: 1%ammonia/10%methanol in DCM) to give the title compound (220mg); MS: 389 (MH+).

Method L

3-(3-Fluorophenyl)-3-(4-Boc-aminophenyl)propionaldehyde

This was prepared from 4-nitro-3'-fluorobenzophenone using a similar sequence of reactions to that used to prepare 3-phenyl-3-(4-Boc-aminophenyl)propionaldehyde from 4-nitrobenzophenone (Method C).

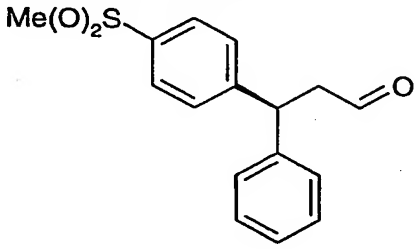
Method M

3-Phenyl-3-(4-methanethiophenyl)propionaldehyde

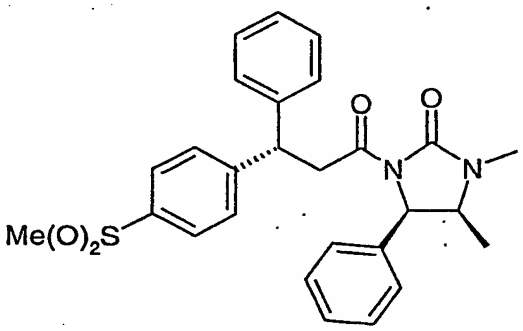
This was prepared from 4-methanethiobenzophenone (Method E) using a similar sequence of reactions to that used to prepare 3-phenyl-3-(4-phenylphenyl)propanionaldehyde from 4-benzoylbiphenyl (Method B).

Method N

(*S*)-3-Phenyl-3-(4-methanesulfonylphenyl)propionaldehyde



Step 1: Preparation of (4*R*, 5*S*)-1-[(*S*)-3-(4-methanesulfonyl-phenyl)-3-phenyl-propionyl]-3,4-dimethyl-5-phenyl-imidazolidin-2-one



To a mixture of copper (I) iodide (960mg, 5.0mmol) and THF (20mL) was added *N,N,N',N'*-tetramethylethylenediamine (0.83mL, 5.5mmol) and the resulting mixture was stirred at room temperature for 10min. then cooled to –78°C. Phenylmagnesium bromide (5.0mL, 1M in THF, 5.0mmol) was added and the resulting mixture stirred at –78°C for 15min. A solution of di-n-butylboron triflate (3.0mL, 1M in diethyl ether, 3.0mmol) and (*E*)-(4*R*, 5*S*)-1-(3-[4-methanesulfonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (Method D, 1.0g, 2.51mmol) in THF (15mL) was added and the resulting mixture was stirred whilst allowing to warm to room temperature for 18h. The reaction mixture was washed with saturated aqueous ammonium chloride, water and brine, dried ($MgSO_4$) and evaporated. The residue was purified by eluting through a 20g Bond Elut with gradient of isohexane to ethyl acetate giving the sub-titled compound (1.49g, 100%); NMR ($CDCl_3$): 0.78 (d, 3H), 2.82 (s,

3H), 3.00 (s, 3H), 3.78 (dd, 1H), 3.80 (m, 1H), 3.98 (dd, 1H), 4.72 (m, 1H), 5.19 (d, 1H), 6.99 (m, 2H), 7.22 (m, 8H), 7.48 (d, 2H), 7.79 (d, 2H); MS: 477 (MH+).

Step 2: Preparation of (*S*)-3-phenyl-3-(4-methanesulfonylphenyl)propan-1-ol

To a solution of (4*R*, 5*S*)-1-[(*S*)-3-(4-methanesulfonyl-phenyl)-3-phenyl-propionyl]-3,4-dimethyl-5-phenyl-imidazolidin-2-one (846mg, 1.78mmol) in THF (20mL) at 0°C was added lithium aluminium hydride (3.6mL, 1M in THF, 3.6mmol) and the resulting mixture was stirred for 15min. The reaction was quenched by the addition of 2M aqueous sodium hydroxide. The phases were separated and the organic phase pre-absorbed onto a Bond Elut and eluted with a gradient of isohexane to ethyl acetate giving the sub-titled compound as a white solid (285mg, 55%); NMR ($CDCl_3$): 1.63 (br s, 1H), 2.33 (m, 2H), 3.00 (s, 3H), 3.59 (t, 2H), 4.28 (t, 1H), 7.23 (m, 5H), 7.43 (d, 2H), 7.82 (d, 2H).

Step 3: Preparation of the title compound

To a solution of (*S*)-3-phenyl-3-(4-methanesulfonylphenyl)propan-1-ol (244mg, 0.84mmol) in DCM (5mL) was added Dess-Martin periodinane (392mg, 0.92mmol) and the resulting mixture was stirred at room temperature for 1.5h. The mixture was washed with 2M aqueous sodium hydroxide (2 x 10mL), dried and evaporated to give the title compound.

Method O

(*R*)-3-(3-fluorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye

This was prepared from (4*R*, 5*S*)-1-(3-[4-methanesulfonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one and 3-fluorophenylmagnesium bromide using a method similar to that used to prepare (*S*)-3-phenyl-3-(4-methanesulfonyl-phenyl)propionaldehyde from phenylmagnesium bromide (Method N); NMR ($CDCl_3$): 3.01 (s, 3H), 3.24 (d, 2H), 4.73 (t, 1H), 6.91 (m, 2H), 6.99 (m, 1H), 7.28 (m, 2H), 7.42 (d, 2H), 7.87 (d, 2H), 9.76 (s, 1H).

Method P

(*S*)-3-(4-fluorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye

This was prepared from (4*R*, 5*S*)-1-(3-[4-methanesulfonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one and 4-fluorophenylmagnesium bromide using a

method similar to that used to prepare (*S*)-3-phenyl-3-(4-methanesulfonyl-phenyl)propionaldehyde from phenylmagnesium bromide (Method N).

Method Q

(*R*)-3-(3-chlorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye

This was prepared from (4*R*, 5*S*)-1-(3-[4-methanesulfonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one and 3-chlorophenylmagnesium bromide using a method similar to that used to prepare (*S*)-3-phenyl-3-(4-methanesulfonyl-phenyl)propionaldehyde from phenylmagnesium bromide (Method N).

Method R

(*R*)-3-(3,4-difluorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye

This was prepared from (4*R*, 5*S*)-1-(3-[4-methanesulfonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one and 3,4-difluorophenylmagnesium bromide using a method similar to that used to prepare (*S*)-3-phenyl-3-(4-methanesulfonyl-phenyl)propionaldehyde from phenylmagnesium bromide (Method N).

Method S

(*S*)-3-(4-methoxyphenyl)-3-(4-methanesulfonylphenyl)propionaldehdye

This was prepared from (4*R*, 5*S*)-1-(3-[4-methanesulfonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one and 4-methoxyphenylmagnesium bromide using a method similar to that used to prepare (*S*)-3-phenyl-3-(4-methanesulfonyl-phenyl)propionaldehyde from phenylmagnesium bromide (Method N).

Method T

(*R*)-3-(3,5-difluorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye

This was prepared from (4*R*, 5*S*)-1-(3-[4-methanesulfonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one and 3,5-difluorophenylmagnesium bromide using a method similar to that used to prepare (*S*)-3-phenyl-3-(4-methanesulfonyl-phenyl)propionaldehyde from phenylmagnesium bromide (Method N).

EXAMPLE 16

The ability of compounds to inhibit the binding of RANTES was assessed by an *in vitro* radioligand binding assay. Membranes were prepared from Chinese hamster ovary cells which expressed the recombinant human CCR5 receptor. These membranes were incubated with 0.1nM iodinated RANTES, scintillation proximity beads and various concentrations of the compounds of the invention in 96-well plates. The amount of iodinated RANTES bound to the receptor was determined by scintillation counting. Competition curves were obtained for compounds and the concentration of compound which displaced 50% of bound iodinated RANTES was calculated (IC_{50}). Preferred compounds of formula (I) have an IC_{50} of less than 50μM.

EXAMPLE 17

The ability of compounds to inhibit the binding of MIP-1α was assessed by an *in vitro* radioligand binding assay. Membranes were prepared from Chinese hamster ovary cells which expressed the recombinant human CCR5 receptor. These membranes were incubated with 0.1nM iodinated MIP-1α , scintillation proximity beads and various concentrations of the compounds of the invention in 96-well plates. The amount of iodinated MIP-1α bound to the receptor was determined by scintillation counting. Competition curves were obtained for compounds and the concentration of compound which displaced 50% of bound iodinated MIP-1α was calculated (IC_{50}). Preferred compounds of formula (I) have an IC_{50} of less than 50μM.

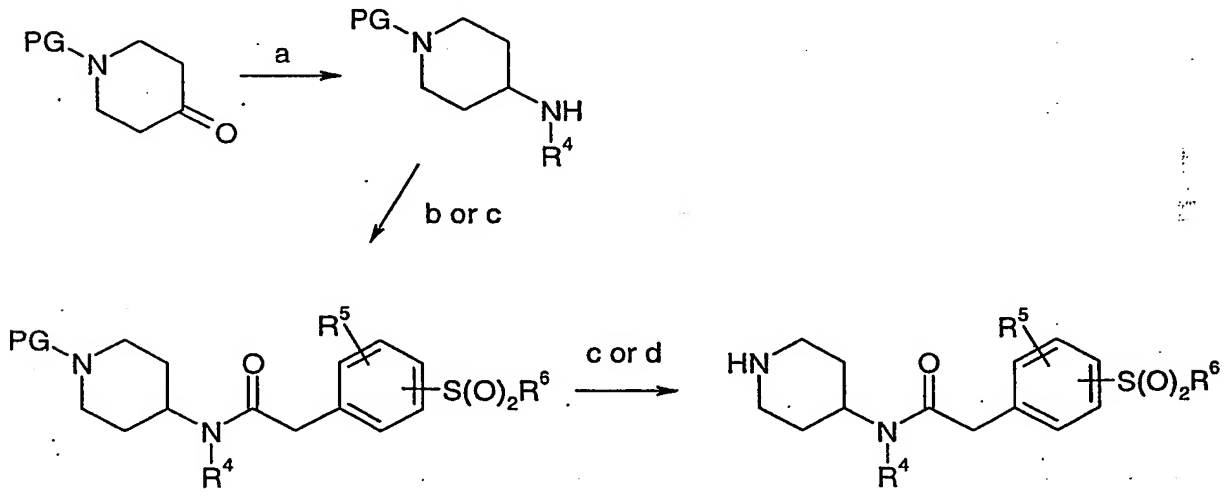
Results from this test for certain compounds of the invention are presented in Table II. In Table II the results are presented as Pic50 values. A Pic50 value is the negative log (to base 10) of the IC_{50} result, so an IC50 of 1μM (that is 1×10^{-6}M) gives a Pic50 of 6. If a compound was tested more than once then the data below is an average of the probative tests results.

Table II

Compound No.	Pic50
28	6.07
40	8.77
41	7.93
42	7.88
43	7.05
44	6.98
45	8.44
46	8.04
47	7.46

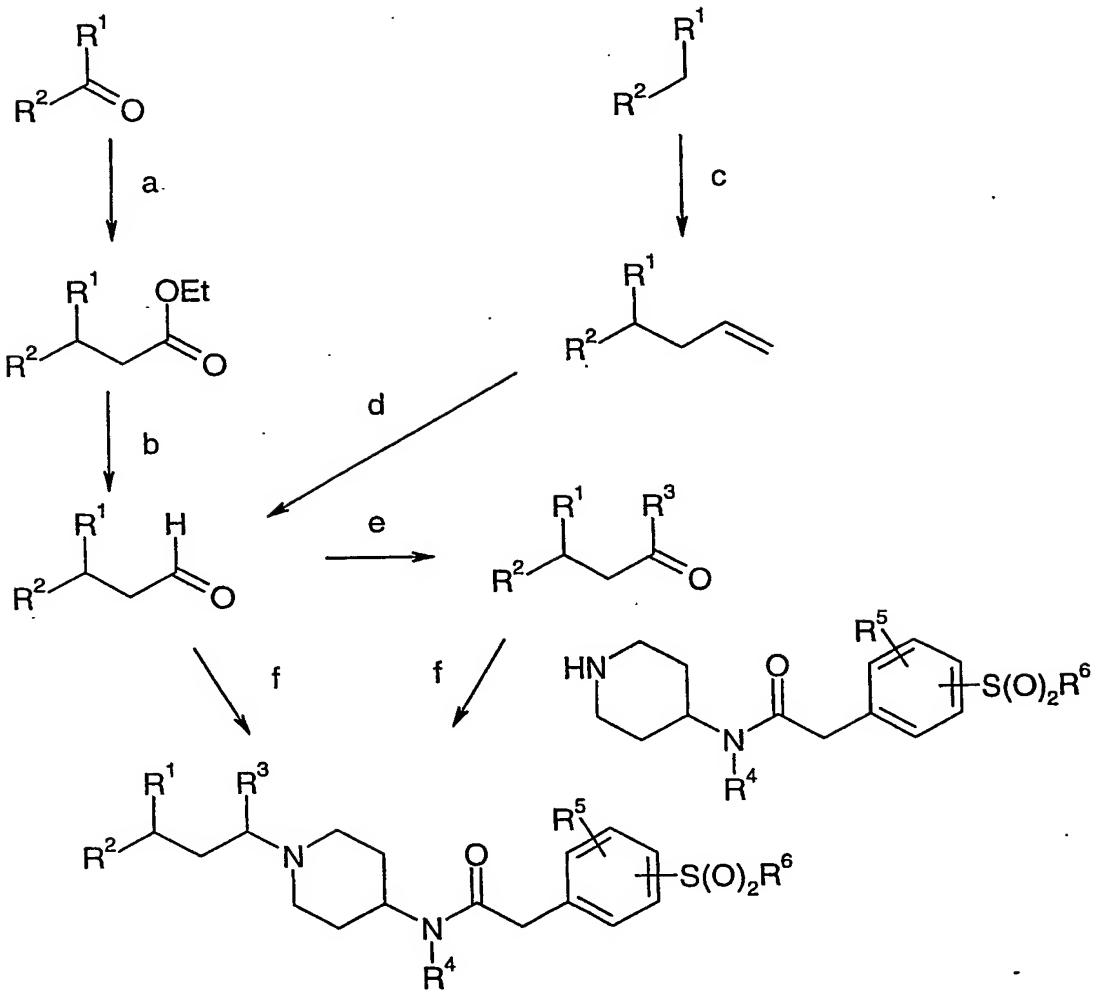
Compound No.	Pic50
48	6.51
49	8.21
50	9.09
51	9.43
52	7.34
53	9
54	7.67
55	6.88
75	7.86

SCHEME 1



Conditions
a) Reductive amination (R^4NH_2, $NaBH(OAc)_3$)
b) Amide formation (acid, coupling agent or acid halide, base)
c) H_2, Pd (when PG is Bn or Bz)
d) HCl or TFA (when PG is Boc)

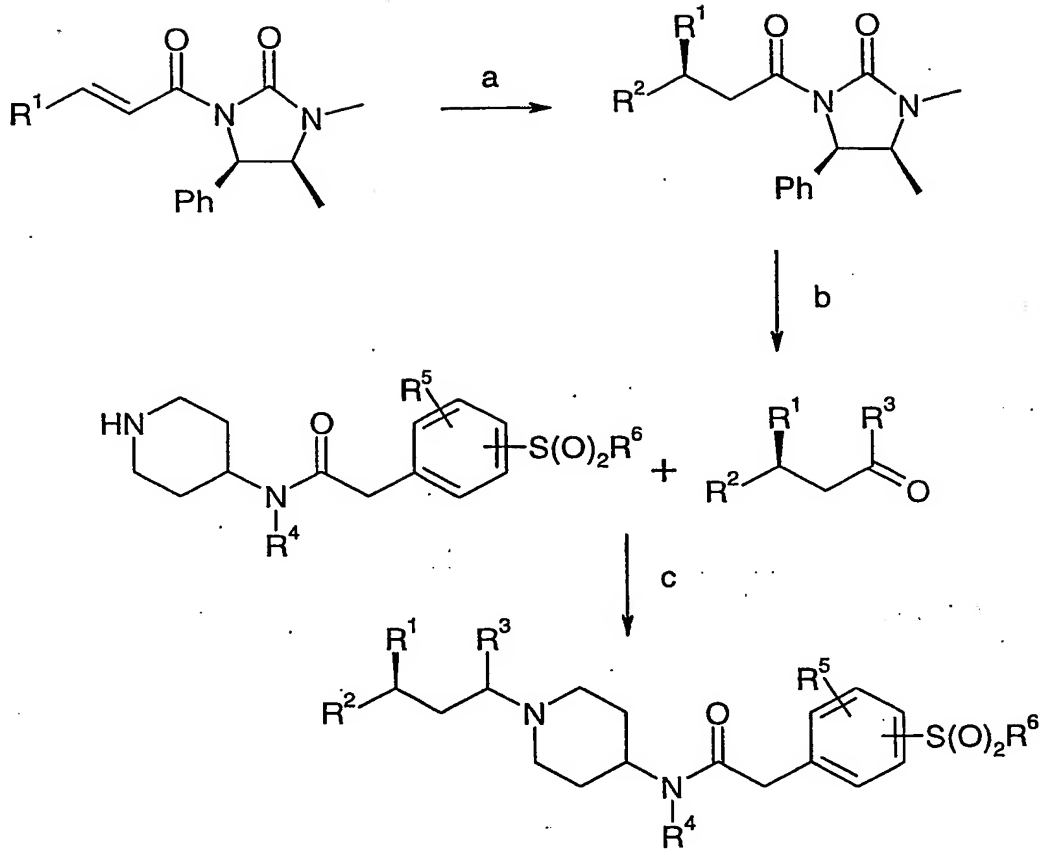
SCHEME 2



Conditions
a) (i) $(EtO)_2P(=O)CH_2CO_2Et$, base; (ii) hydrogenation (e.g. $Pd(OH)_2$, H_2)
b) (i) Reduction (e.g. $LiAlH_4$); (ii) Oxidation (e.g. Dess-Martin periodinane)
c) Allyl bromide, base (e.g. LDA)
d) O_3 then Me_2S
e) (i) R^3MgBr (ii) Oxidation
f) Reductive amination ($NaBH(OAc)_3$, AcOH)

5

SCHEME 3



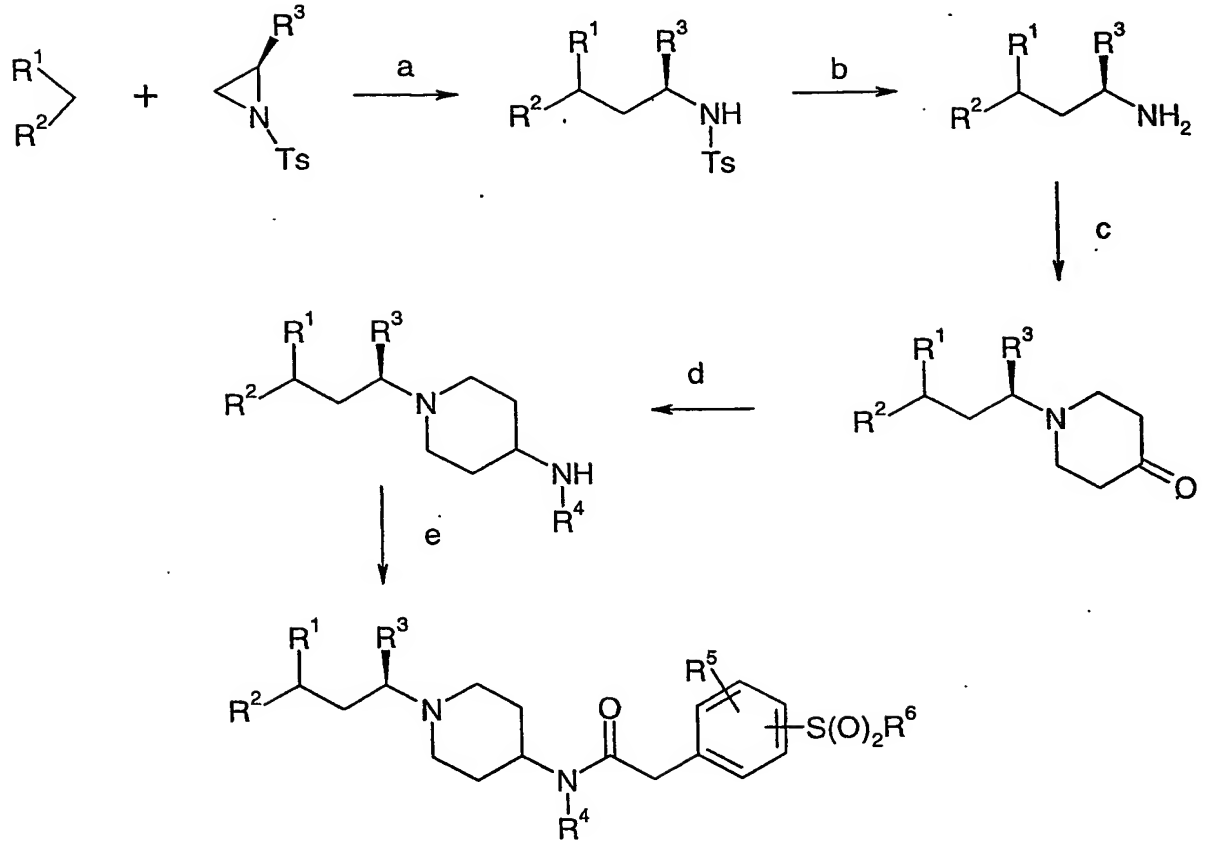
Conditions

a) R^2MgBr, CuI, TMEDA, n-Bu_2BOTf

b) Reduction-oxidation (for when R^3 is H), or Reduction-oxidation then R^3MgBr (for when R^3 is alkyl) then oxidation

c) Reductive amination ($NaBH(OAc)_3$, AcOH)

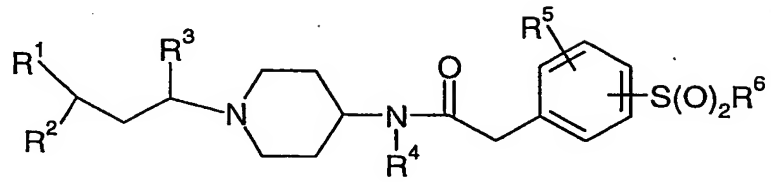
SCHEME 4



Conditions
a) Base (e.g. LDA)
b) Deprotection (e.g. HBr/AcOH)
c) 1-Methyl-1-ethyl-4-oxopiperidinium iodide, K_2CO_3
d) Reductive amination (R^4NH_2, $NaBH(OAc)_3$, AcOH)
e) Amide formation (acid & coupling agent)

CLAIMS

1. A compound of formula (I):



(I)

wherein:

R^1 is phenyl {para-substituted by: halo, hydroxy, nitro, $S(O)_k(C_{1-6}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-6}$ alkyl), $S(O)_2N(C_{1-6}$ alkyl)$_2$, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, $C(O)NH_2$, $C(O)NH(C_{1-6}$ alkyl), $C(O)N(C_{1-6}$ alkyl)$_2$, C(O)[N-linked heterocyclyl], CO_2H, $CO_2(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), $C(O)(C_{1-6}$ alkyl), CF_3, OCF_3, phenyl, heteroaryl, (C_{1-4} alkyl)phenyl, (C_{1-4} alkyl)heteroaryl, NHC(O)phenyl, NHC(O)heteroaryl, $NHC(O)(C_{1-4}$ alkyl)phenyl, $NHC(O)(C_{1-4}$ alkyl)heteroaryl, $NHS(O)_2$phenyl, $NHS(O)_2$heteroaryl, $NHS(O)_2(C_{1-4}$ alkyl)phenyl, $NHS(O)_2(C_{1-4}$ alkyl)heteroaryl, $NHC(O)NH(C_{1-6}$ alkyl), $NHC(O)NH(C_{3-7}$ cycloalkyl), NHC(O)NHphenyl, NHC(O)NHheteroaryl, $NHC(O)NH(C_{1-4}$ alkyl)phenyl or $NHC(O)NH(C_{1-4}$ alkyl)heteroaryl; wherein the foregoing phenyl and heteroaryl groups are optionally substituted by halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3};

R^2 is phenyl or heteroaryl, either of which is optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3;

R^3 is hydrogen or C_{1-4} alkyl;

R^4 is ethyl, allyl or cyclopropyl;

R^5 is hydrogen, halo, hydroxy, nitro, $S(O)_m(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3;

R^6 is C_{1-4} alkyl;

k, m and n are, independently, 0, 1 or 2;

or a pharmaceutically acceptable salt thereof or a solvate thereof;

provided that:

- when R^3 and R^5 are both hydrogen, R^4 is ethyl, R^6 is para-$(S(O)_2CH_3)$ and R^2 is unsubstituted phenyl then R^1 is not para-methoxy-phenyl, para-methyl-phenyl, para-trifluoromethyl-phenyl or 3,4-dichlorophenyl;
- when R^3 and R^5 are both hydrogen, R^4 is ethyl, R^6 is para-$(S(O)_2CH_3)$ and R^2 is unsubstituted phenyl, pyrid-2-yl or pyrid-4-yl then R^1 is not para-chloro-phenyl; and,
- when R^3 and R^5 are both hydrogen, R^6 is para-$(S(O)_2CH_3)$ and R^2 is meta-chloro-phenyl, unsubstituted phenyl or thiophen-3-yl then R^1 is not para-fluoro-phenyl.

2. A compound as claimed in claim 1 wherein R^1 is phenyl {para-substituted by: halo, $S(O)_k(C_{1-6}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-6}$ alkyl), $S(O)_2N(C_{1-6}$ alkyl$)_2$, cyano, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, $CO_2(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), NHC(O)phenyl, NHC(O)heteroaryl, $NHC(O)(C_{1-4}$ alkyl)phenyl, $NHC(O)(C_{1-4}$ alkyl)heteroaryl, $NHS(O)_2$phenyl, $NHS(O)_2$heteroaryl, $NHS(O)_2(C_{1-4}$ alkyl)phenyl, $NHS(O)_2(C_{1-4}$ alkyl)heteroaryl, $NHC(O)NH(C_{1-6}$ alkyl), $NHC(O)NH(C_{3-7}$ cycloalkyl), NHC(O)NHphenyl, NHC(O)NHheteroaryl, $NHC(O)NH(C_{1-4}$ alkyl)phenyl or $NHC(O)NH(C_{1-4}$ alkyl)heteroaryl; wherein the foregoing phenyl and heteroaryl groups are optionally substituted by halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}; and k is 2.

3. A compound as claimed in claim 1 wherein R^2 is phenyl, mono-fluorophenyl, difluorophenyl, mono-chlorophenyl or mono-$(C_{1-4}$ alkoxy)phenyl.

4. A compound as claimed in claim 1 wherein R^3 is hydrogen.

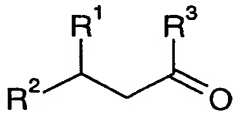
5. A compound as claimed in claim 1 wherein R^4 is ethyl.

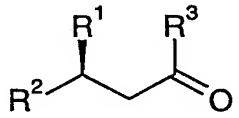
6. A compound as claimed in claim 1 wherein R^5 is hydrogen, halo, hydroxy, nitro, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 or OCF_3.

7. A compound as claimed in claim 1 wherein R^6 is C_{1-4} alkyl and wherein the $S(O)_2R^6$ group of formula (I) is para disposed to the remainder of the structure of formula (I).

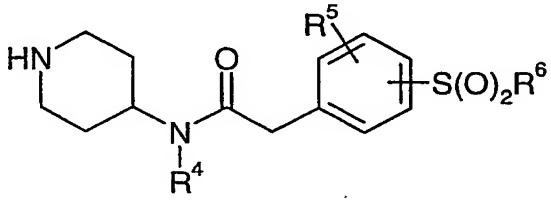
8. A process for the preparation of a compound as claimed in claim 1, the process comprising:

a) reductive amination of a compound of formula (II) or (IIa):


(II)

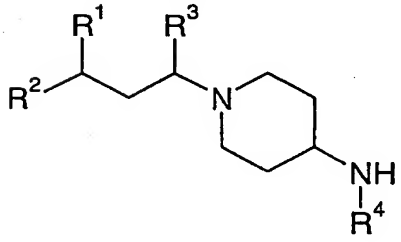

(IIa)

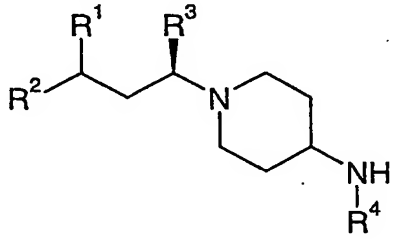
with a compound of formula (III):


(III)

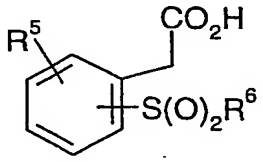
in the presence of $NaBH(OAc)_3$ (wherein Ac is $C(O)CH_3$) and acetic acid, in a suitable solvent at room temperature; or,

b) coupling a compound of formula (IV) or (IVa):


(IV)


(IVa)

with a compound of formula (V):


(V)

in the presence of a suitable coupling agent, in the presence of a suitable base, in a suitable solvent and at room temperature (for example 10-30°C).

9. A pharmaceutical composition which comprises a compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof or solvate thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

10. A compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof or solvate thereof, for use as a medicament.

11. A compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof or solvate thereof, in the manufacture of a medicament for use in therapy.

12. A method of treating a CCR5 mediated disease state comprising administering to a patient in need of such treatment an effective amount of a compound as claimed in claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/02054

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 211/58, C07D 401/06, C07D 409/06, C07D 413/06, C07D 417/06, A61K 31/4523, A61P 11/00, A61P 17/00 A61P 19/00, A61P 29/00, A61P 37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA, EPO-INTERNAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0187839 A1 (ASTRAZENECA AB), 22 November 2001 (22.11.01), see particularly compound 44, page 31 --	1-12
X	WO 0114333 A1 (ASTRAZENECA UK LIMITED), 1 March 2001 (01.03.01), see claims and page 20, line 26 - page 22, line 10 --	1-12
X	WO 9925686 A1 (TEIJIN LIMITED), 27 May 1999 (27.05.99), see claims and page 1, line 5 - line 15 --	1-12

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 February 2003	11 -02- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer NEBIL GECER/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/02054

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT.

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1013276 A1 (PFIZER INC.), 28 June 2000 (28.06.00), see claims and page 30, line 9 - line 11 -- --------	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/02054

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claim 12 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/12/02

International application No.
PCT/SE 02/02054

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0187839 A1	22/11/01	AU 5898101 A	26/11/01
		GB 0011838 D	00/00/00
WO 0114333 A1	01/03/01	AU 6461600 A	19/03/01
		EP 1212299 A	12/06/02
		SE 9902987 D	00/00/00
WO 9925686 A1	27/05/99	AU 744685 B	28/02/02
		AU 1374199 A	07/06/99
		BG 104441 A	31/01/01
		BR 9814645 A	31/07/01
		CA 2309328 A	27/05/99
		CN 1279668 T	10/01/01
		EE 200000294 A	15/08/01
		EP 1030840 A	30/08/00
		HR 20000214 A	31/12/01
		HU 0004200 A	28/03/01
		IL 135488 D	00/00/00
		JP 2001523661 T	27/11/01
		NO 20002486 A	18/07/00
		NZ 503782 A	28/03/02
		PL 342207 A	21/05/01
		SK 5532000 A	12/02/01
		TR 200001399 T	00/00/00
		US 6451842 B	17/09/02

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/12/02

International application No.
PCT/SE 02/02054

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1013276 A1	28/06/00	AP 200102186 D	00/00/00
		AP 200102187 D	00/00/00
		AU 1290400 A	31/07/00
		AU 1675100 A	31/07/00
		BG 105709 A	28/02/02
		BG 105721 A	28/02/02
		BR 9916585 A	16/10/01
		BR 9917007 A	30/10/01
		CN 1331591 T	16/01/02
		CN 1331691 T	16/01/02
		EE 200100344 A	15/10/02
		EP 1140085 A	10/10/01
		EP 1140920 A	10/10/01
		GB 9828420 D	00/00/00
		HR 20010478 A	30/06/02
		HU 0104795 A	29/04/02
		HU 0104910 A	28/10/02
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		IL 143512 D	00/00/00
		JP 2000212159 A	02/08/00
		JP 2002533393 T	08/10/02
		JP 2002533461 T	08/10/02
		NO 20013149 A	23/08/01
		NO 20013183 A	08/08/01
		PL 349091 A	01/07/02
		PL 349495 A	29/07/02
		TR 200101793 T	00/00/00
		TR 200101867 T	00/00/00
		TR 200200938 T	00/00/00
		WO 0038680 A	06/07/00
		WO 0039125 A	06/07/00
		GB 9922702 D	00/00/00

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 May 2003 (22.05.2003)

PCT

(10) International Publication Number
WO 2003/042177 A1

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(21) International Application Number:
PCT/SE2002/002054

(22) International Filing Date:
12 November 2002 (12.11.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(48) Date of publication of this corrected version:
6 January 2005

(15) Information about Correction:
see PCT Gazette No. 01/2005 of 6 January 2005, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PIPERIDINE DERIVATIVES AND THEIR USE AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY (ESPECIALLY CCR5)

(57) Abstract: Compounds of formula (I): compositions comprising them, processes for preparing them and their use in medical therapy (for example modulating CCR5 receptor activity in a warm blooded animal).

WO 2003/042177 A1